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The Synthesis and Characterization of a Polymer-Supported Cellulose Model

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THE SYNTHESIS AND CHARACTERIZATION OF A POLYMER-SUPPORTED CELLULOSE MODEL

A thesis submitted by

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ABSTRACT

Most of what is known about glycosidic bond cleavage in cellulose has been obtained from the study of simple soluble glycosides and oligosaccharides. However, cellulose differs from these model compounds in two ways. First, cellulose is insoluble in alkaline pulping liquors and hence subject to heterogeneous reactions. Second, the freedom of the individual anhydroglucose units is severely restricted in cellulose compared to the model compounds.

In this study, an insoluble (solid-supported) cellulose model was prepared by condensing the C-4' hydroxyl group of an allyl protected disaccharide, 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3,6-tri-O-allyl-β-D-glucopyranosyl)-D-glucitol, with an iodomethylated polystyrene resin and removing the allyl protecting groups. The preparation of the allyl protected disaccharide from cellobiose octaacetate required ten steps and employed a combination of allylate, acetate, and benzylidene protecting groups. The yield of the allylated disaccharide based on the starting cellobiose octaacetate was 5%.

The loading of the disaccharide on the polymer was determined by treating the supported model with osmium tetraoxide, prior to removal of the allyl protecting groups, and measuring the resin's increase in weight. Osmium tetraoxide reacts quantitatively with allyl ethers to form osmylate esters. The loading was confirmed by hydrolyzing the supported model's glycosidic linkage, after removal of the allyl protecting groups, and measuring the amount of 1,5-anhydro-D-glucitol, the aglycon, released into the liquid phase. The loading determined by these two methods was 0.22 millimole of 1,5-anhydrocellobiitol per gram of resin.

The C-4' point of attachment was verified by a methylation-hydrolysis technique. The supported model was exhaustively methylated and the model's

glycosidic and disaccharide-polymer linkages were hydrolyzed. The hydrolysis products were reduced and then acetylated to yield 4-O-acetyl-1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol from the aglycon and 1,4,5-tri-O-acetyl-2,3,6-tri-O-methyl-D-glucitol from the glycon. The product from the glycon was indicative of the C-4' point of attachment.

The stability of the benzyl ether linkage was verified by preparing and degrading methyl 4-O-benzyl-α-D-glucopyranoside. The rate of glycosidic bond cleavage in 1,5-anhydrocellobiitol at 170°C in 2.5N sodium hydroxide was at least 180 times faster than the rate of benzyl-oxygen bond cleavage in methyl 4-O-benzyl-α-D-glucopyranoside under similar conditions.

The polymer-supported model developed in this thesis should provide a new tool for studying heterogeneous glycosidic bond cleavage in cellulose.

INTRODUCTION

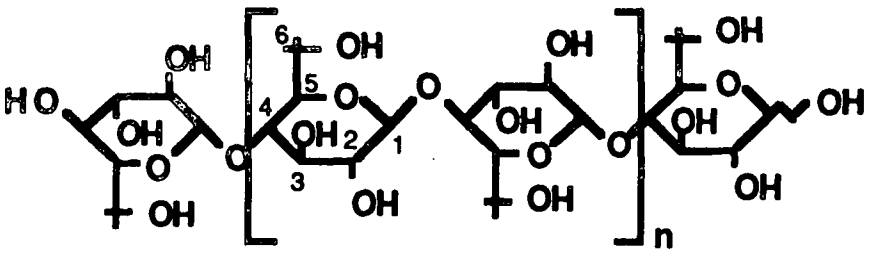
PERSPECTIVE

The primary objective in the pulping of wood is to liberate the fibers for use in the manufacturing of paper and cellulosic products. In alkaline pulping this is accomplished by chemically removing the lignin. Unfortunately alkali is not specific for lignin. It also reacts with the polysaccharide constituents resulting in pulps of lower yield and quality. A more complete understanding of the reactions of cellulose in the alkaline pulping process could potentially lead to pulps of higher yield and quality. This investigation has been directed toward developing a simple heterogeneous model system for studying the alkaline degradation of cellulose.

BACKGROUND

Cellulose

Cellulose is a linear polymer of D-glucopyranose in which the individual units are linked by a β-D-glucosidic bond from C-1 of one unit to C-4 of the next unit (Fig. 1). The stereochemical relationship between the substituents on C-1 and C-2 is trans. The average degree of polymerization (DP) of native cellulose is estimated to be between 5,000 and 10,000. The two end groups are nonequivalent and are referred to as the reducing and nonreducing ends. The reducing end of the cellulose chain has a hydroxyl group at C-1 while the non-reducing end has a hydroxyl group at C-4. Native cellulose contains both crystalline and amorphous regions.



nonreducing end reducing end

Figure 1. Representation of cellulose.

The alkaline degradation of cellulose is thought to occur primarily in the amorphous regions involving the following reactions: swelling of the fiber, dissolution (and reprecipitation) of low DP polysaccharides, sequential loss (peeling) of monomers from the reducing end of the polysaccharide, and random cleavage of the glycosidic bonds. The peeling reaction has been studied in detail and results in lower carbohydrate yields.[1,2] The peeling reaction continues until it is prevented chemically by the formation of a metasaccharinic acid group at the reducing end of the cellulose chain or physically by the crystalline structure of the cellulose.[3a,4] On the average, 50 to 65 glucose units are lost before the cellulose chain is stabilized by the stopping reactions.[5] Unfortunately the cellulose chain is never truly stabilized to the peeling reaction since the random cleavage of the glycosidic bonds creates new reducing ends. Matthews[6] has shown that peeling from these new reducing ends accounts for up to one-fifth of the polysaccharide lost. In addition, chain cleavage significantly decreases the cellulose's degree of polymerization which affects paper strength properties and also produces low molecular weight, alkali-soluble material.

Glycosidic bond cleavage in cellulose may occur at either the glycosyl-oxygen bond or the oxygen-aglycon bond (Fig. 2). A critical study of glycosidic bond cleavage in cellulose is not easy, since the cleavage reaction cannot be separated from the other alkaline reactions. Because of this, attempts to

understand random chain cleavage have centered on the study of model compounds. These compounds have generally been simple mono- and disaccharides which, unlike cellulose, are soluble in alkaline pulping liquors.

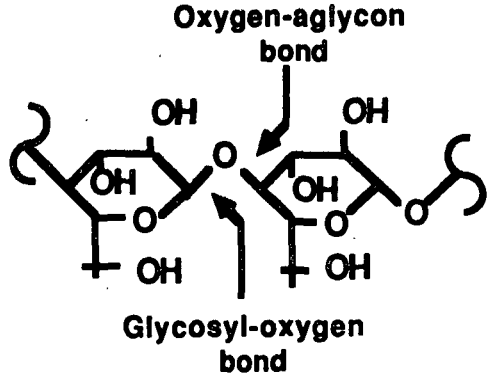


Figure 2. Glycosyl-oxygen and oxygen-aglycon bonds in cellulose.

Model Compound Studies

Monosaccharides

Montgomery and coworkers[7] demonstrated that phenyl β-D-glucopyranoside (trans-1,2 configuration) is rapidly degraded by hot alkali (1.3N potassium hydroxide, 100°C), while phenyl α-D-glucopyranoside (cis-1,2 configuration) is not. Similarly, McCloskey and Coleman[8] showed that phenyl 3-O-methyl-β-D-glucopyranoside is readily hydrolyzed by alkali, while phenyl 2,3-di-O-methyl-β-D-glucopyranoside is not. In order to rationalize these observations, McCloskey and Coleman[8] proposed a neighboring group mechanism for the degradation of phenyl β-D-glucopyranoside (1) (Fig. 3). The first step in this mechanism is the reversible ionization of the C-2 hydroxyl group. This is followed by the nucleophilic displacement of the phenoxyl aglycon by the C-2 alkoxide ion to form a 1,2-anhydride (3). The anhydride is a reactive intermediate and has never been isolated. It may be opened by the C-6 alkoxide ion to form 1,6-anhydro-β-D-glucopyranose (5) (levoglucosan) or by hydroxide ion to yield D-glucose (6).

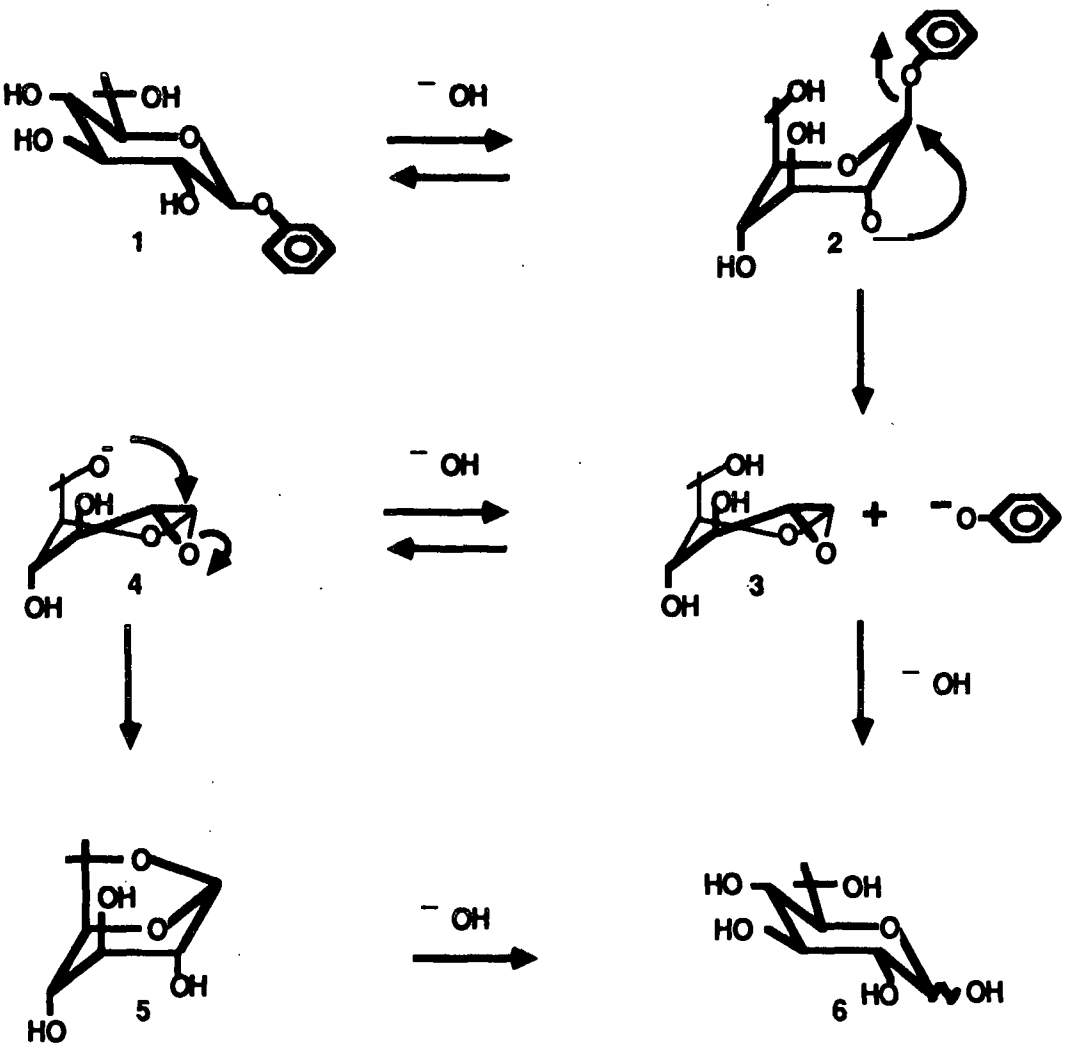


Figure 3. McCloskey-Coleman mechanism proposed for the alkaline degradation of phenyl β-D-glucopyranoside (1).[8]

Levoglucosan is much more stable in hot alkali than D-glucose and has been isolated in high yield (88%) from the alkaline degradation of phenyl β-D-glucopyranoside.[7] The formation of levoglucosan in the degradation of other trans-1,2 glycosides has been taken as an indication that the McCloskey-Coleman mechanism is operating.[9,11,15,16]

For the McCloskey-Coleman mechanism to operate the hydroxyl group on C-2 must be available for ionization and located trans diaxial to the phenoxyl group on C-1. Phenyl β-D-glucopyranoside requires a change from the $^4C_1$ to the $^1C_4$ conformation in order to obtain the required diaxial relationship. However, the mechanism is blocked in phenyl 2,3-di-O-methyl-β-D-glucopyranoside since the C-2 substituent cannot be ionized and also in phenyl α-D-glucopyranoside since it does not have the required trans-1,2 configuration.

Alkaline degradation of alkyl glycosides requires much more rigorous conditions (2.5N sodium hydroxide, 170°C) than the aryl glycosides. Lindberg[10] investigated the alkaline degradation of several methyl glycosides. In each case, the trans-1,2 anomer was more reactive than the corresponding cis-1,2 anomer. However, the difference in cis-trans reactivity was much smaller than for aryl glycosides.[7,10]

Nault[11] demonstrated that only 30% of methyl β-D-glucopyranoside (trans-1,2 configuration) degrades to form levoglucosan. This low yield of levoglucosan, and the small difference in cis-trans reactivity, suggest the presence of secondary reaction pathways. These pathways are capable of competing with the McCloskey-Coleman mechanism in the trans-1,2 glycosides and replacing it in those glycosides where it cannot function.

Nault[11] proposed the McCloskey-Coleman mechanism for the primary pathway in the degradation of methyl β-D-glucopyranoside and a mixture of S_N1* and S_N2** mechanisms for the secondary pathways. Nault was unable to determine the relative importance of the secondary pathways. In the S_N1 mechanism, the glycosidic

*The S_N1 notation signifies a unimolecular nucleophilic substitution.
**In the S_N2 notation the 2 signifies bimolecular.

bond is heterolytically cleaved to yield a carboxonium ion at C-1 (Fig. 4). The carboxonium ion can then be attacked by either hydroxide ion to give D-glucose (6) or the C-6 alkoxide ion to give the 1,6-anhydride (5). The S_N2 mechanism is a one step mechanism (Fig. 5). It involves direct nucleophilic attack of hydroxide ion at the anomeric carbon to displace the aglycon. An S_N2 mechanism has also been proposed for the degradation of methyl α-D-glucopyranoside and methyl 2-O-methyl-β-D-glucopyranoside.[11,12]

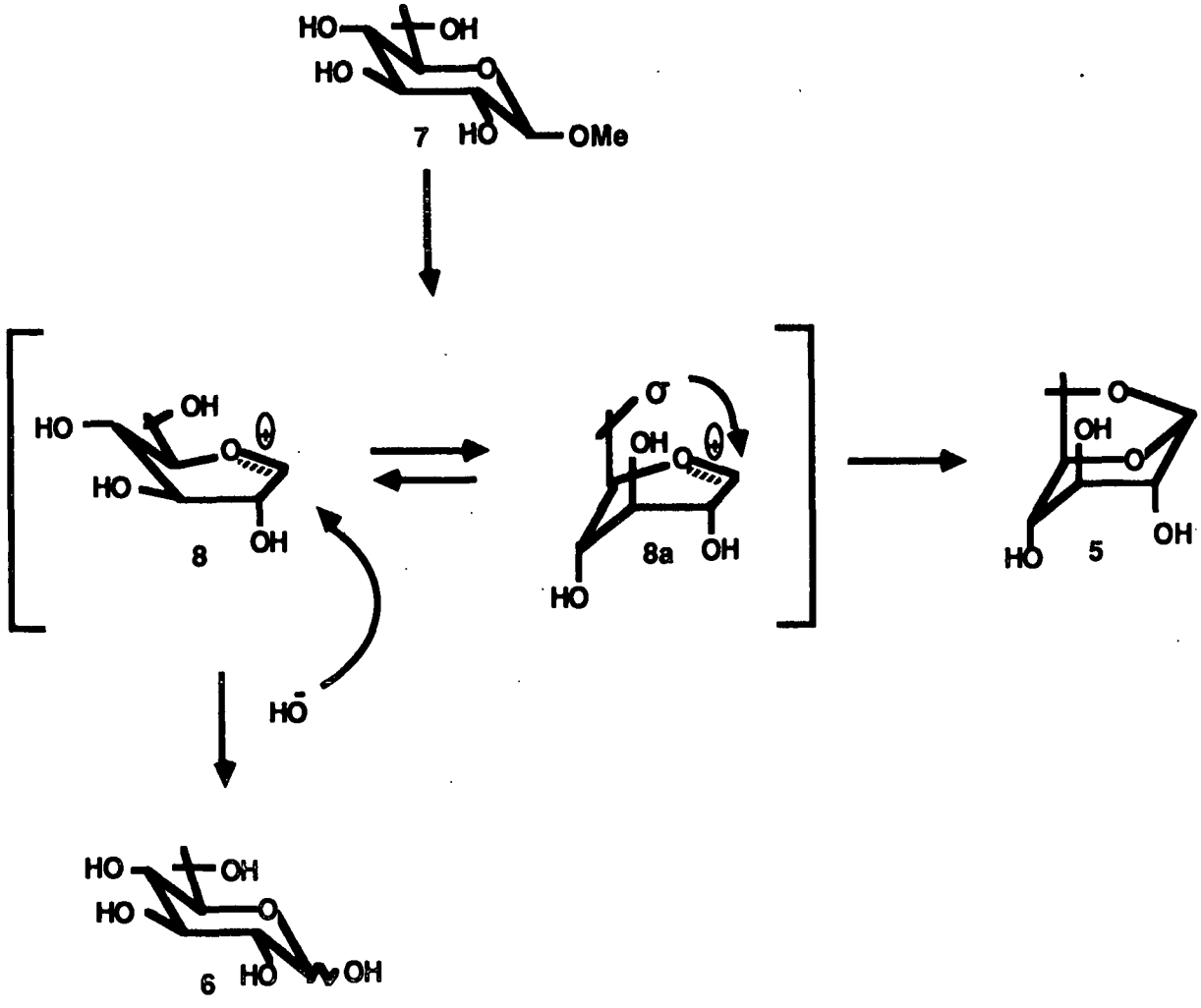


Figure 4. Proposed S_N1 mechanism for the degradation of β-D-glucopyranoside (7).[11]

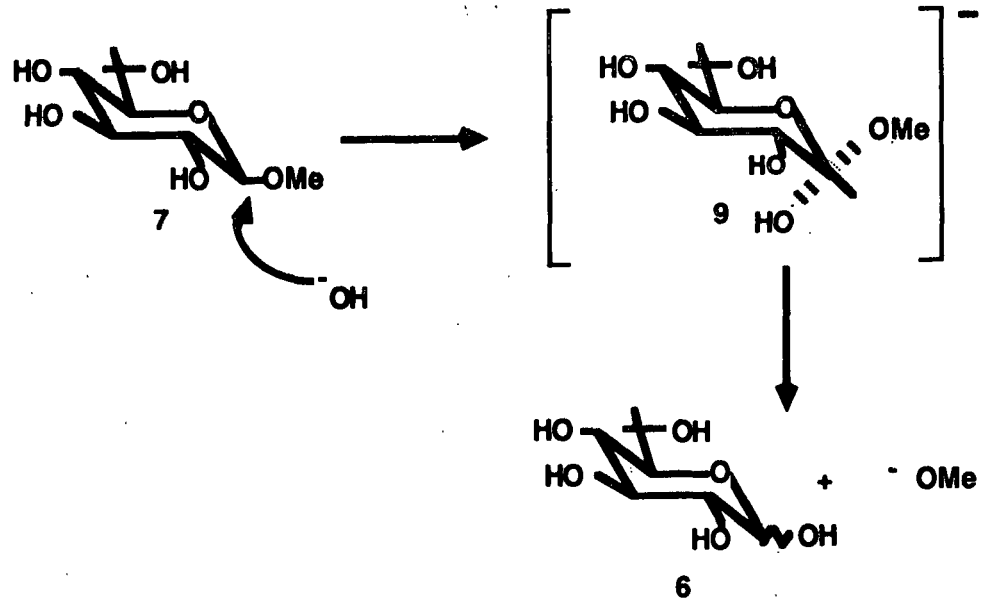


Figure 5. Proposed S_N2 mechanism for the alkaline degradation of methyl β-D-glucopyranoside (7).[11]

Janson and Lindberg[13] investigated the alkaline degradation of methyl furanosides. They proposed an $S_N1cB(2)ro$* mechanism to account for the formation of methyl α-L-arabinopyranoside from the alkaline degradation of methyl α-L-arabinofuranoside. In general, the furanosides which have a trans-1,2 configuration react much faster than the corresponding pyranosides.[80] Thus, although methyl α-L-arabinofuranoside and methyl α-L-arabinopyranoside are both trans-1,2 glycosides, methyl α-L-arabinopyranoside is less reactive than methyl α-L-arabinofuranoside and can be isolated.

The first step in the $S_N1cB(2)ro$ mechanism is the reversible ionization of the C-2 hydroxyl group (Fig. 6). This is followed by a nucleophilic attack of the C-2 alkoxide ion on C-1 to displace the ring oxygen and form a 1,2-epoxide (12). The epoxide is then opened by hydroxide to yield a reducing group or by

*The $S_N1cB(2)ro$ notation signifies the ring opening via unimolecular nucleophilic substitution by the conjugate base of the C-2 hydroxyl group.

the C-5 alkoxide ion to form methyl α-L-arabinopyranoside (13). Janson and Lindberg isolated only trace amounts of the pyranoside (1%). Reactions of this type might also be responsible for glycosidic bond cleavage in cellulose.[17]

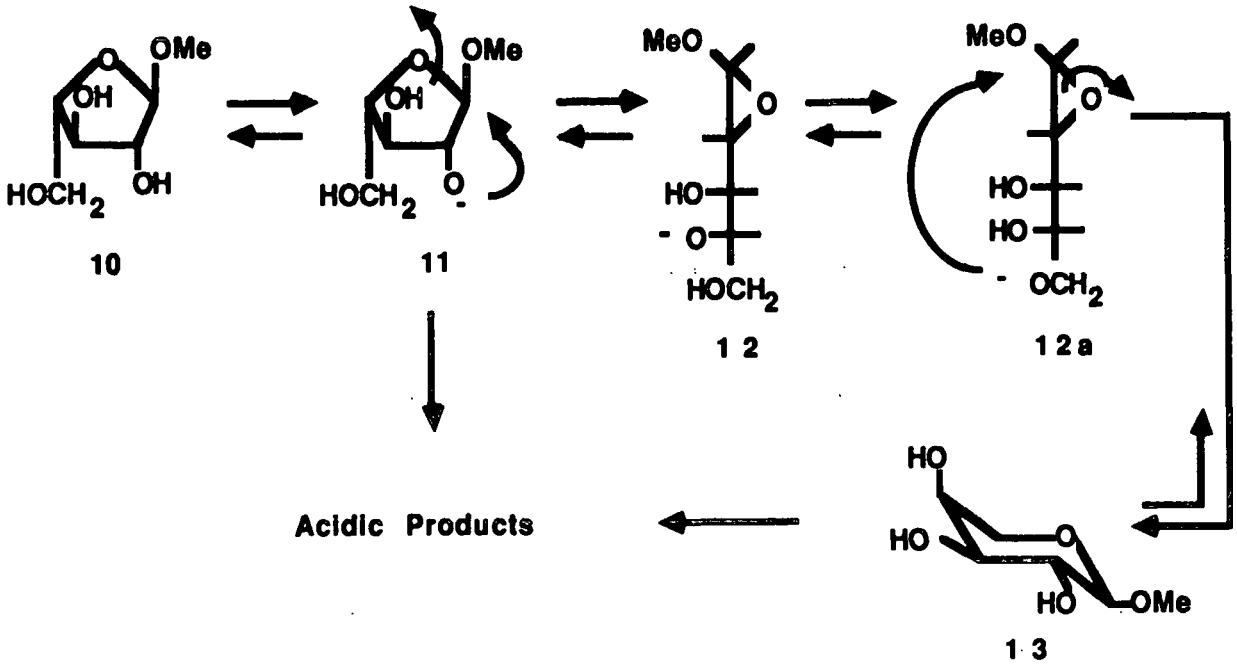


Figure 6. Proposed $S_N1cB(2)ro$ mechanism for the formation of methyl α-L-arabinopyranoside (13) from methyl α-L-arabinofuranoside (10).[13]

The alkaline degradation of methyl α- and β-D-glucopyranoside in oxygen-18 enriched water has shown that a small amount of oxygen-aglycon bond cleavage (5 to 10%) occurs.[11,14] This cleavage increases with the addition of a stronger nucleophile such as hydrosulfide ion.[15] A direct nucleophilic attack on the aglycon via an S_N2 mechanism has been proposed to explain this oxygen-aglycon cleavage.

Disaccharides

Brandon et al.[16] investigated the alkaline degradation of 1,5-anhydro-4-O-β-D-glucopyranosyl-D-glucitol (1,5-anhydrocellobiitol). Their findings supported those of the earlier studies on the alkyl glycosides in that cleavage can

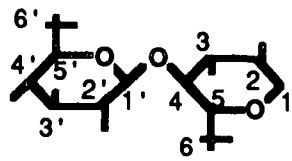
occur at either the glycosyl-oxygen bond or the oxygen-aglycon bond. Cleavage of the glycosyl-oxygen bond dominated, accounting for approximately 80-90% of the degradation and resulting in a 35% yield of levoglucosan.

Although the formation of levoglucosan was taken as an indication that the McCloskey-Coleman mechanism was operating, its low yield in Brandon's study suggested that, like the alkyl glycosides, there were alternative reaction pathways available for the degradation of 1,5-anhydrocellobiitol. Attempts have been made to identify these pathways.[15,16,17,18]

Also, like the alkyl glycosides, the differences in the cis-trans reactivity of the disaccharides were smaller than the aryl glycosides. For example, the rates of disappearance of 1,5-anhydro-4-O-α-D-glucopyranosyl-D-glucitol[16] and 1,5-anhydro-4-O-β-D-mannopyranosyl-D-mannitol[17] were approximately five times slower than 1,5-anhydrocellobiitol. In addition neither of the 1,6-anhydrides, levoglucosan or levomannosan, were observed. A mixture of S_N1 and $S_N1cB(2')ro$* mechanisms has been proposed for the degradation of these compounds.[17,18] Both mechanisms can also operate in the 1,5-anhydrocellobiitol case.

Blythe et al.[15] demonstrated that the rate of a kraft and a soda degradation of 1,5-anhydrocellobiitol were essentially the same. He also showed that the hydrogen sulfide ion present in a kraft cook is a stronger nucleophile than hydroxide ion at 170°C. Since the rate of an S_N2 mechanism is dependent on the

*The numbers associated with the dimer shown below indicate the system used to designate a disaccharide's carbon atoms.



nucleophilicity of the attacking species, an S_N2 mechanism for glycosyl-oxygen bond cleavage was ruled out.

The oxygen-aglycon bond in 1,5-anhydrocellobiitol is cleaved 10-20% of the time.[16] Brandon proposed that this cleavage occurred by an S_N1 mechanism. The aglycon C-4 cation formed 1,5:3,6-dianhydro-D-galactitol (19) or degraded rather than forming 1,5-anhydro-D-galactitol (20) or 1,5-anhydro-D-glucitol (21) (Fig. 7).

An S_N2 mechanism for oxygen-aglycon bond cleavage was ruled out on the basis of a product analysis which showed that only a trace amount of 1,5-anhydro-D-galactitol, the expected S_N2 product, was formed.[16] Similarly, an $S_N1cB(3)$ mechanism was rejected since the amount of oxygen-aglycon bond cleavage in 1,5-anhydrocellobiitol and 1,5-anhydro-2,3,6-tri-O-methyl-4-O-β-D-glucopyranosyl-D-glucitol were essentially the same (see Fig. 8).

From these studies it is apparent that a variety of pathways are available for the degradation of the model compounds. These compounds are soluble in alkaline pulping liquors. However, cellulose is insoluble in alkali and thus subject to heterogeneous reactions. Our understanding of glycosidic bond cleavage in cellulose is limited by our lack of studies involving heterogeneous reactions.

Heterogeneous Reactions

In general the rate of a heterogeneous reaction is slower than the analogous homogeneous reaction.[19,20] Often this is the result of mass transfer limitations.[19a] However, it may also be the result of differences in the inherent reactivities of the reactants.[21,22] A simple example is the slower rate of ester hydrolysis by resin bound acid than by free acid. Hammett et al.[21] has

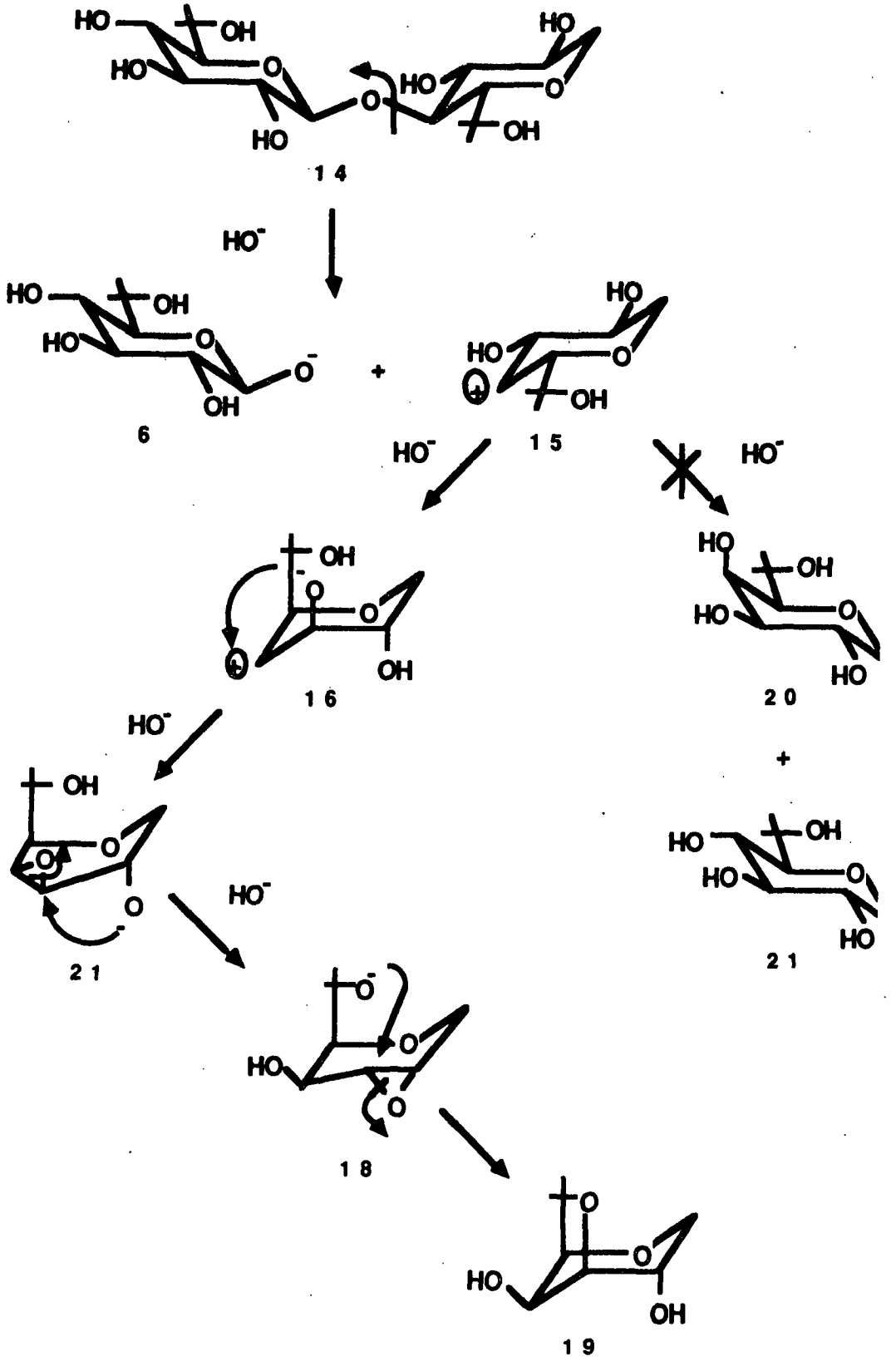


Figure 7. Proposed S_N1 mechanism for the cleavage of the oxygen-aglycon bond in 1,5-anhydrocellobiitol (14).

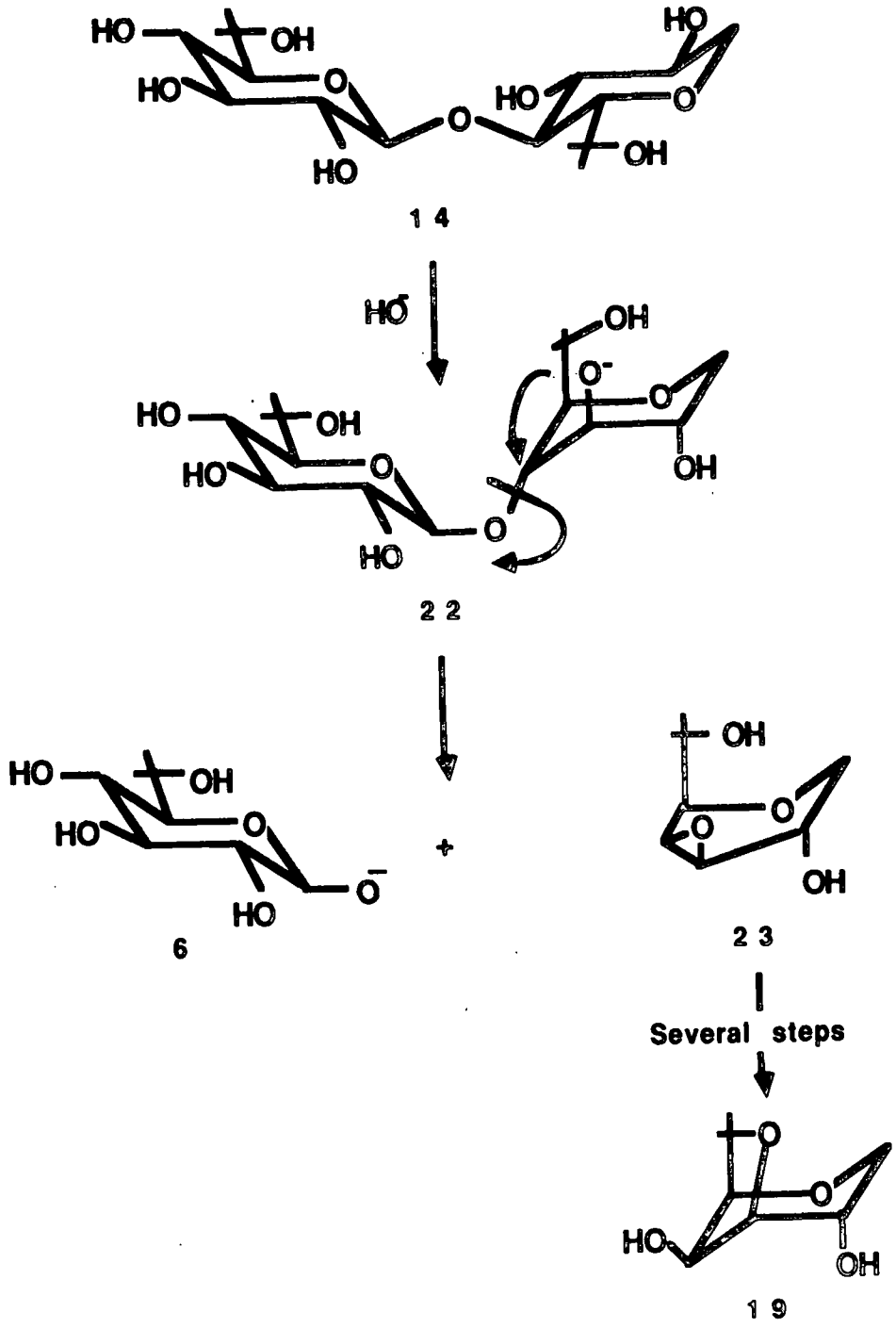


Figure 8. Potential $S_N1cB(3)$ mechanism for the alkaline degradation of 1,5-anhydrocellobiitol (14).[16]

shown that this difference is not related to diffusion of the ester through the resin but is dependent on the internal entropy of the ester. The rate difference was smaller in cyclic esters than in linear esters (Table 1). Hammett[21] suggested that the losses in internal degrees of freedom in forming a transition state between the resin and the ester were greater than the losses in forming a transition state between the free acid and the ester. Therefore the intrinsic rate constant for the resin-catalyzed reaction is less. This also explained the smaller differences in reactivity of the cyclic esters than the linear esters since the cyclic esters have less entropy to lose.

Table 1. Hydrolysis of esters by 0.466N HCl and by IR-120 resin.[21]

Ester	Temperature, °C	$K_H \times 10^6$, sec	$K_R \times 10^6$, sec	K_R/K_H
Methyl acetate	25.0	54.4	27.2	0.502
Ethyl acetate	25.0	46.4	15.0	0.326
Ethyl n-butyrate	25.0	19.2	2.56	0.134
Methyl n-octanoate	25.0	16.8	0.948	0.056
Methyl cyclopentane-carboxylate	25.0	24.0	3.47	0.144

K_H = rate constant for free acid hydrolysis.
K_R = rate constant for resin bound acid hydrolysis.

Changes in the inherent reactivity can also be caused by electrostatic effects. An example of this is the ionization of carboxylic acid groups in a polyacrylic acid.[19b,23,24] The acidity of the individual carboxylic groups decreases as the degree of ionization increases. This decrease in reactivity is attributed to the polymer backbone becoming more negatively charged. A second example is the base-catalyzed hydrolysis of polymethylacrylamide.[23,25] Only a

fraction of the amide groups are readily cleaved. The remainder are unreactive. This decrease in reactivity has been explained by the polymer backbone becoming more negatively charged and thereby excluding the hydroxide ion.

Polymer-Supported Synthesis

The use of solid supports in organic chemistry was pioneered by Merrifield.[26] In 1963 he reported an unconventional method of polypeptide synthesis. It differed from the general methods in that one reagent was covalently bound to an insoluble support. This functionalized support was then reacted with a series of dissolved reactants to give a polymer-bound polypeptide. The support was then isolated from the reaction mixture by filtration and the peptide was released by cleavage of the polymer peptide bond.

The main advantage in Merrifield's synthesis was the ease of isolation and purification of the intermediates. All that was required for the supported materials were simple filtrations and extractions. Prior to Merrifield's work the objective of polymer reactions was modification or improvement of the polymer structure. Since this work, polymer supports have been used in the synthesis of several complex organic molecules.[19,20]

There are two possible approaches to solid phase synthesis of oligosaccharides.[19c,20] These approaches differ in the position by which the polymer is attached to the sugar and the type of glycosylating agent used to lengthen the chain. For example, in the first approach,[19c,20] a protected sugar is attached to the support via its anomeric center (C-1) (Fig. 9). Next, one of the hydroxyl groups is selectively deprotected and condensed with a dissolved glycosylating agent. The chain is then lengthened by repeating the deprotection and condensation steps.

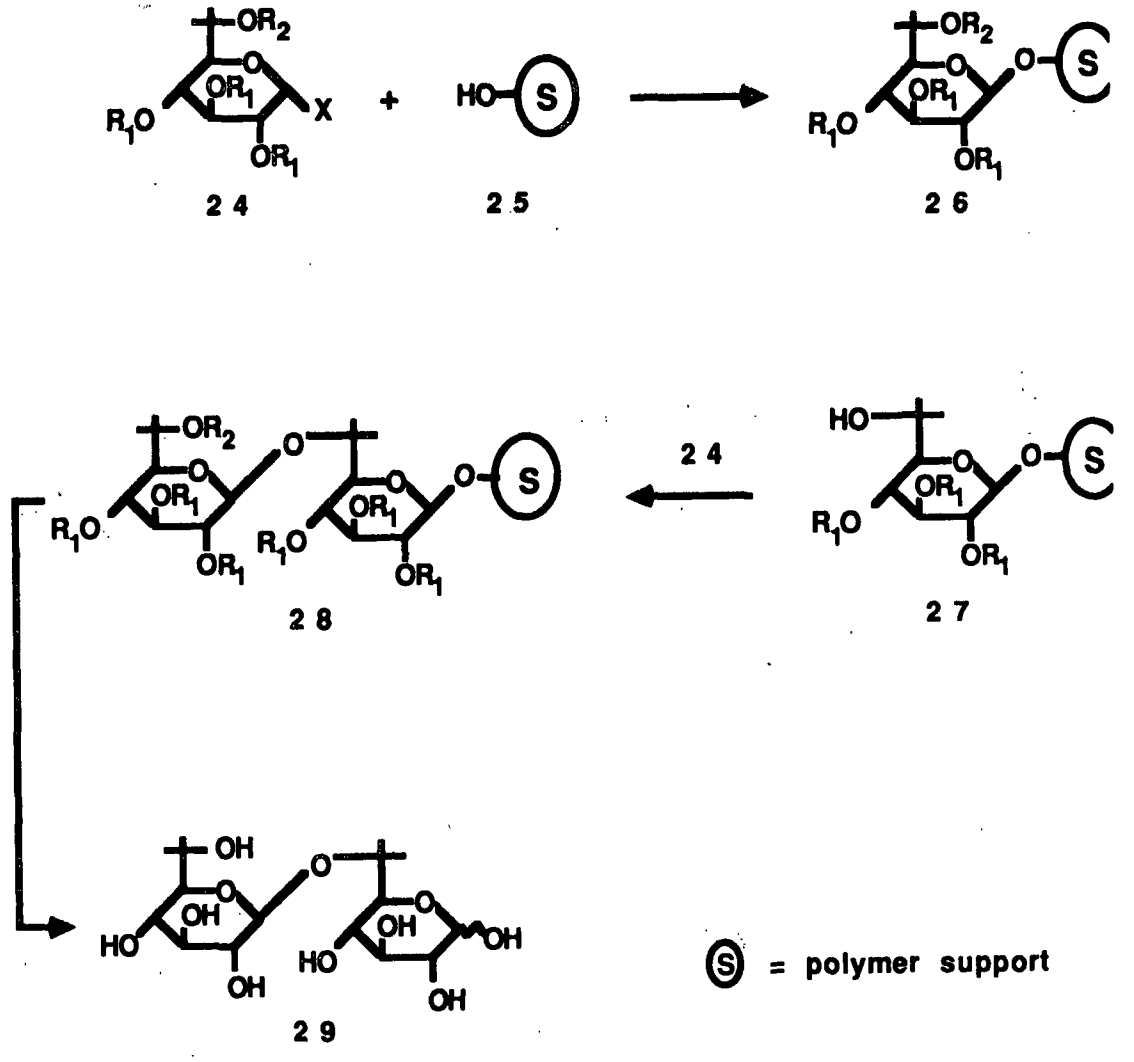


Figure 9. Polymer-supported oligosaccharide synthesis - attachment through a glycosidic linkage.[19c,20]

In the second approach,[19c,20] the first sugar is coupled to the polymer support by an ester bond through one of its hydroxyl groups (Fig. 10). The C-1 position is then activated to form a supported glycosylating agent and reacted with the free hydroxyl of a protected dissolved sugar. The chain is then lengthened by repeating the activation and condensation steps. Solid supported syntheses of several oligosaccharides have been reported (Table 2).

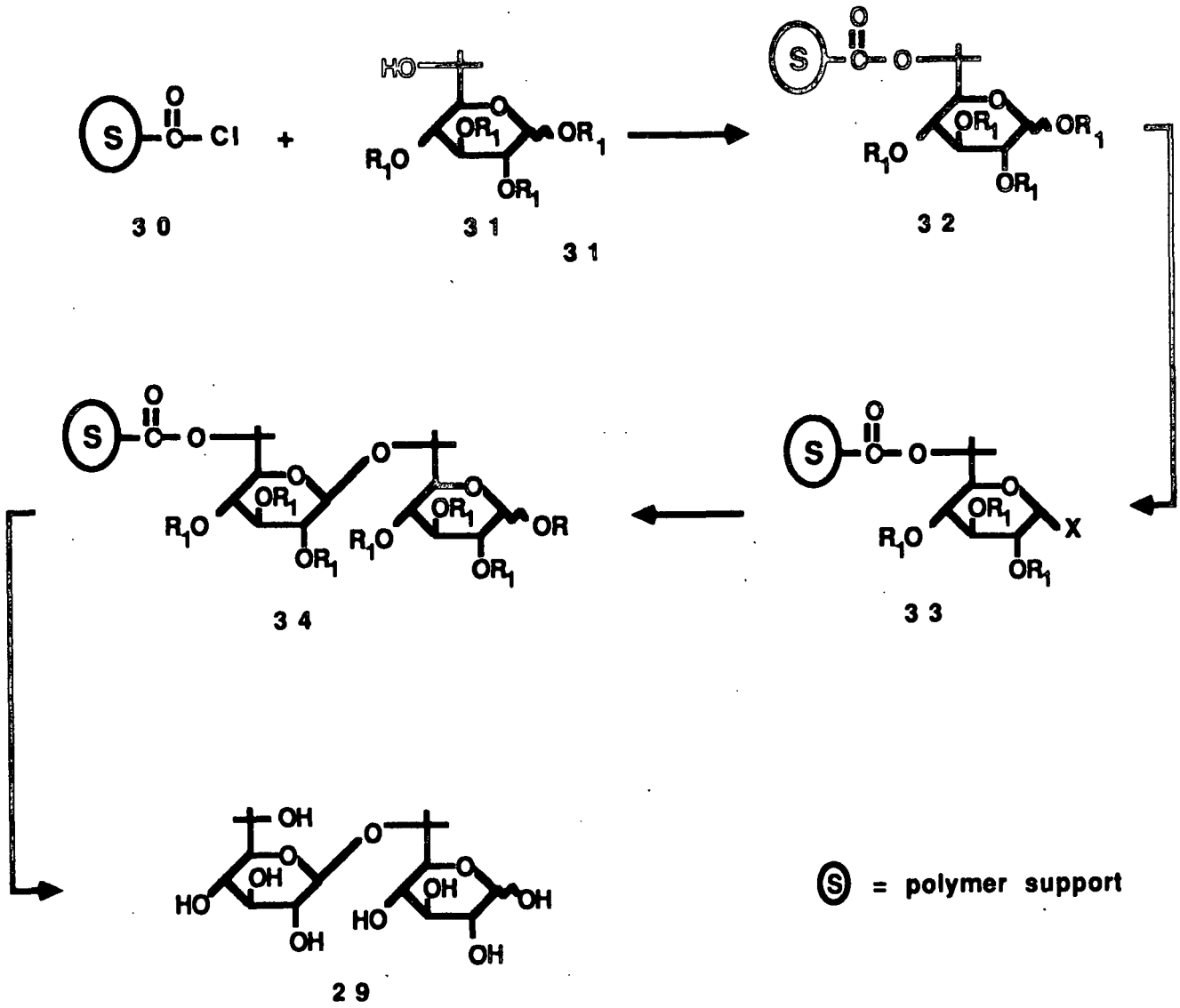


Figure 10. Polymer-supported oligosaccharide synthesis- attachment through a nonglycosidic linkage.[19c,20]

The use of polymer supports in the field of carbohydrate chemistry has not been limited to oligosaccharide synthesis. Supports have also been used in the preparation of partially substituted monosaccharides. Supports incorporating benzylaldehyde, boric acid, and trityl chloride have been used to prepare supported benzylidene acetals, boronate esters, and trityl ethers, respectively, of several simple sugars.[19d] These polymer-bound sugars were then esterified or etherified and removed from the support to yield the desired products (Table 3).

Table 2. Polymer-supported oligosaccharide synthesis.

Polymer Support (Functional Group)	Type of Polymer-Sugar Bond (Site of Bonding)	Oligosaccharide Prepared	Reference
Polystyrene ($-CH=CH-CH_2OH$)	Glycoside	Isomaltose	27
Polystyrene [$-C_6H_2(O-NO_2)-(m-OMe)CH_2OH$]	Glycoside	Isomaltose	28
Polystyrene ($-COCl$)	Ester (C-3)[a]	2-Acetamido-6-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-6-D-glucopyranosyl)-2-deoxy-β-D-glucopyranoside[b]	29,30
Polystyrene ($-COCH_2CH_2COOH$)	Ester (C-1)	Gentiotetrose	31
Polystyrene ($-SO_3Cl$)	Sulfonate ester (C-6)	Gentiobiose	32
Glass ($-C_6H_4CH_2Br$)	Glycoside	Isomaltose	19
Polystyrene ($-CH_2Cl$ or $-CH_2SH$)	Thioglycoside	Isomaltose	33

[a]Also used an ester linkage through C-6.
[b]Also prepared analogous 1,3-linked disaccharide.

Polymer-supported synthesis of mono- and oligosaccharides offer the same advantages as in polypeptide synthesis, namely, the ease of purification and isolation of the supported intermediates.

Table 3. Polymer-supported protecting groups.

Polymer Support (Functional Group)	Type of Polymer-Sugar Bond	Product (Yield)	Reference
Polystyrene [$C(Ph)_2Cl$]	Tritylether	Methyl 2,3,4-tr-O-acetyl-α-D-glucopyranoside (75%)	34
Polystyrene (-CHO)	Benzylidene acetal	Methyl 2,3-di-O-benzoyl-α-D-glucopyranoside (80%)	35,36
Polystyrene (-CHO)	Benzylidene acetal	Methyl 2,3-di-O-benzyl-α-D-glucopyranoside (40%)	35
Polystyrene [$-B(OH)_2$]	Borate ester	Methyl 4-O-benzoyl-α-L-rhamnopyranoside (83%)	37
Polystyrene [$-B(OH)_2$]	Borate ester	Methyl 2,3-di-O-benzoyl-α-D-glucopyranoside (88%)	37

[a]Products listed were selected as representative samples.

Styrene-Based Polymers

Although a wide range of supports (often called resins) are available, the majority of supported reactions have employed styrene-based polymers. A random survey of nearly 100 supported reactions conducted by Mathur, et al.[20] revealed that about 80% of the polymers used were based on styrene. Unlike most other supports, polystyrene is easily functionalized, stable at high temperatures, and resistant to chemical attack. In addition it can be purchased with a wide range of swelling characteristics and pore dimensions.

Most polystyrene resins are prepared by suspension polymerization of styrene and divinyl benzene.[19e,20] Gel type resins are prepared without the aid of a solvent. The polymer chains are solvated by the unreacted monomers. As the

monomers are consumed, the polymer chains collapse, forming a nonporous matrix. These resins retain very little porosity in the dry state. Resins with enhanced porosity are prepared by adding a solvent to the polymerization suspension. The solvent prevents the polymer chains from collapsing. These resins retain a large portion of their porous structure in the dry state. If the solvent is a good solvent for the monomers and the polymer, the resin is referred to as macroporous. However, if it is a good solvent for the monomers but a poor solvent for the polymer, the resin is referred to as macroreticular.

The polymer's swelling characteristics, and to a certain extent its pore sizes, can be controlled by regulating the degree of cross-linking.[19-20]* For instance, the degree of cross-linking in swellable resins or gels is usually less than ten percent and most often below two percent. The pore dimensions of swellable resins are influenced by the solvent employed, being maximum in good solvents. On the other hand, in nonswellable rigid resins the pore sizes are independent of the solvent. The degree of cross-linking in these resins is usually greater than twenty percent.

Highly cross-linked macroreticular resins have the advantage that they absorb both good and bad solvents but the disadvantage of low loading capacities.[19f] As the amount of divinyl benzene is increased in the polymerization suspension, the polymer chains become entangled, creating regions within the support which are not available for functionalization. In the highly cross-linked resins, only the pore surfaces are available as reaction sites. In contrast, in lightly cross-linked resins virtually all the aromatic rings are available for functionalization.

*The degree of cross-linking is the percentage of backbone substituents which are interlinked.

THESIS OBJECTIVE

Attempts have been made to compare paper properties to the cellulose degree of polymerization (DP).[3b] In general it is found that the paper strength decreases with decreasing DP of the cellulose. Random chain cleavage during alkaline pulping significantly reduces the cellulose DP.

Most of what is known about the mechanisms of glycosidic bond cleavage in cellulose has been obtained from the study of model compounds. These compounds are generally simple glycosides or oligosaccharides which are soluble in the alkaline media. However, cellulose is not soluble in pulping liquor and hence is subject to heterogeneous reactions. Any attempt to extend our knowledge of soluble bond cleavage to cellulose is limited by our lack of understanding of heterogeneous reactions.

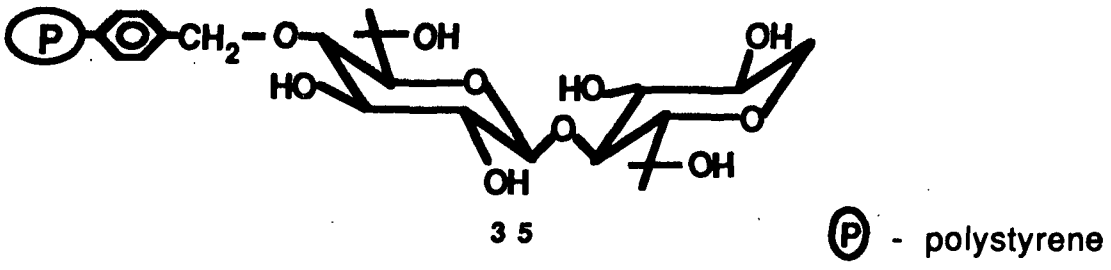
The McCloskey-Coleman mechanism has been proposed to account for the degradation of trans-1,2 glycosides. A key step in this mechanism for the β-D-glucosides is the change from the $^4C_1$ to the $^1C_4$ conformation. This occurs fairly rapidly in the simple model compounds. However, how readily it occurs in cellulose is uncertain, since the freedom of the individual anhydroglucose units is severely restricted by the physical structure of the cellulose.

The objective of this thesis was to prepare a solid supported cellulose model which would remain insoluble in the pulping liquor and would restrict the motion of the glycosyl ring. This model could then be used to study glycosidic bond cleavage under heterogeneous reaction conditions.

RESULTS AND DISCUSSION

MODEL DESIGN CRITERIA

The model selected consists of a 1,5-anhydrocellobiitol unit attached through its C-4' position to a macroreticular polystyrene support by a benzyl ether linkage (Fig. 11).



35

Figure 11. Polymer-supported 1,5-anhydrocellobiitol.

The 1,5-anhydrocellobiitol was chosen because of its similarity to cellulose. This compound is a simple cellulose model in that it contains only one glycosidic linkage and no reducing end group. It should only undergo glycosidic bond cleavage. Also, its homogeneous degradation under both kraft and soda conditions has been the subject of previous studies.[15,16]

A macroreticular polystyrene, Amberlite XE-305, was chosen for the support on the basis of its assumed compatibility with and resistance to alkali. These resins contain a large permanent pore structure which should allow the penetration of the cooking liquor throughout the support. In addition, polystyrene is resistant to alkaline attack and stable at high temperatures (250°C).[38]

Clearly, the polymer-model linkage had to be stable under the conditions to be used in the degradation studies. Carbohydrate methyl ethers are stable at 170°C in 2.5N sodium hydroxide.[11,39] In contrast, under the same conditions the

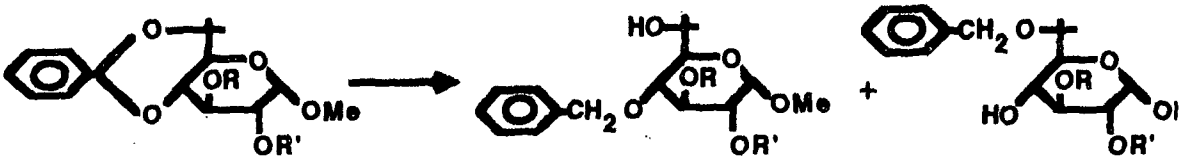
polymeric acetal and esters employed in the synthesis and derivation of mono- and oligosaccharides would be subject to alkaline hydrolysis. A benzyl ether was selected because it permits the removal of the supported material for analysis, and the chemical properties of benzyl ethers are very similar to those of the methyl ethers.[40]

Finally, attachment through the C-4' position was chosen to simulate the 1-4 linkage in cellulose. Obviously, the polystyrene does not resemble cellulose. However, it should act as a large bulky substituent, restricting the motion of the glycosyl ring.

SYNTHETIC APPROACH

In planning a synthesis it is helpful to work backward by first examining the product's carbon skeleton and functional groups for recognizable units and then mentally breaking it apart into those units. The model is a solid-supported 4'-O-benzyl ether of 1,5-anhydrocellobiitol.

Syntheses of benzyl ethers have been reviewed.[40,41] Carbohydrate 4-O- and 6-O-benzyl ethers can be prepared by the reduction of 4,6-O-benzylidene acetals.[42,43,44] Studies on monosaccharides indicate that the direction of the benzylidene ring cleavage is determined by the bulk of the 3-O-substituent.[42] For example, reduction of methyl 3-O-benzyl-4,6-O-benzylidene-α-D-glycopyranoside (**36**) gave only the 4-O-benzyl derivative while reduction of methyl 4,6-O-benzylidene-α-D-glucopyranoside (**38**) resulted in a mixture of the 4-O- and 6-O-benzyl compounds (3:2) (Fig. 12). Thus, the C-3 hydroxyl group must be blocked in order to obtain the 4-O-benzyl ether.



36 = R = Bn, R'= H
38 = R = R' = H
41 = R = R' = pMeOBn

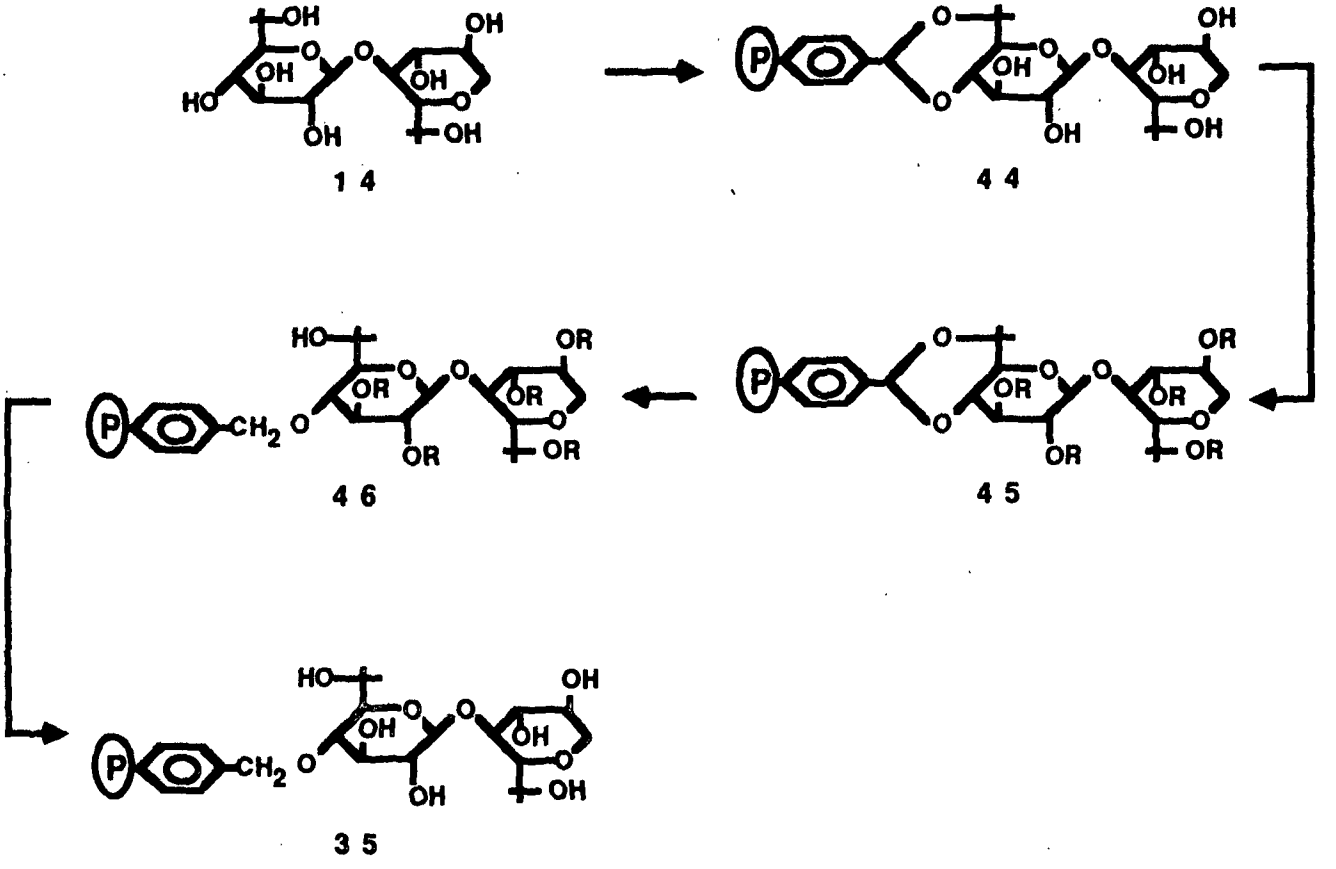
37 = R = R' = Bn
39 = R = R' = H
42 = R = R' = pMeOBn

40 = R = R' = H
43 = R = R' = pI

Figure 12. Formation of benzyl ethers by reduction of benzylidene acetal.

In this approach (Scheme 1) the 1,5-anhydrocellobiitol would be attached directly to the polymer support by a benzylidene acetal. The free hydroxyl groups would then be blocked and the benzylidene group would be reduced to the 4'-O-benzyl ether linkage.

Scheme 1



While Scheme 1 appears conceptually easy, its execution proved difficult. Test reductions on methyl 4,6-O-benzylidene-2,3-di-O-p-methoxybenzyl-α-D-glucopyranoside (41) gave a mixture of two products (≈ 2:1) even though the C-3 hydroxyl group was blocked as a p-methoxybenzyl ether. The major product was isolated and identified as the 4-O-benzyl ether 42 (Fig. 12). The minor product was not identified. This product could pose a significant problem. Unlike the products from the homogeneous reaction, the products from the reduction of the supported benzylidene cannot be separated by simple chromatographic techniques. Both products would remain attached to the polymer. Thus, this approach was not pursued further.

Carbohydrate benzyl ethers can also be prepared by treating the carbohydrate's hydroxyl group first with a base and then with a benzyl halide. Unfortunately this method is not specific for the preparation of 4-O-benzyl ethers. That is, simply mixing a supported benzyl halide with 1,5-anhydrocellobiitol and alkali would not result in the desired product. Instead a mixture of products would be obtained, each varying in the position that the polymer is attached to the 1,5-anhydrocellobiitol. The major products would be attached through the more reactive primary hydroxyl groups, the C-6 and C-6'.

In order to obtain only the 4'-O-substituted product 35, it was necessary to first block the other hydroxyl groups with protecting groups. Protecting groups are used to mask a functional group while a reaction is carried out. They must be capable of being formed in high yield, of surviving the projected reaction conditions, and of being released at the appropriate time. Also, they must not interfere with the reaction site.

Potential protecting groups were tested by preparing methyl 4-O-benzyl-α-D-glucopyranoside (49) from various 2,3,6-tri-O-substituted derivatives of methyl α-D-glucopyranoside (Fig. 13). Attempts to prepare 49, employing p-methoxybenzyl ethers, benzoate esters, and acetate esters as protecting groups, were unsuccessful. However, the desired product was prepared using allyl ether protecting groups. Allyl ethers have been used in the synthesis of specifically benzylated carbohydrate derivatives.[45,46,47] They are obtained in high yield by treating the carbohydrate first with a base and then with an allyl halide. They are removed by isomerization to prop-1-enyl ethers and subsequent acid hydrolysis.

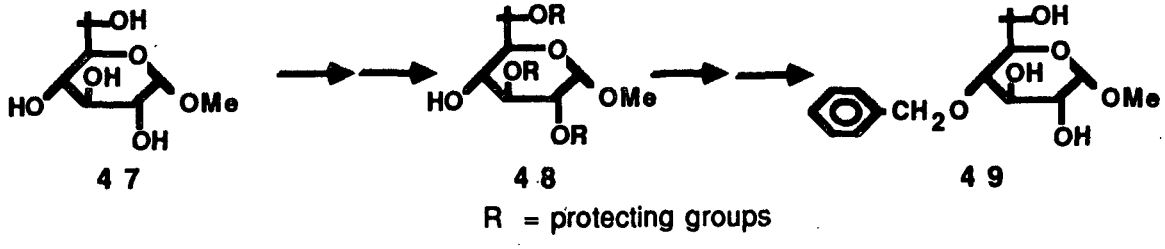
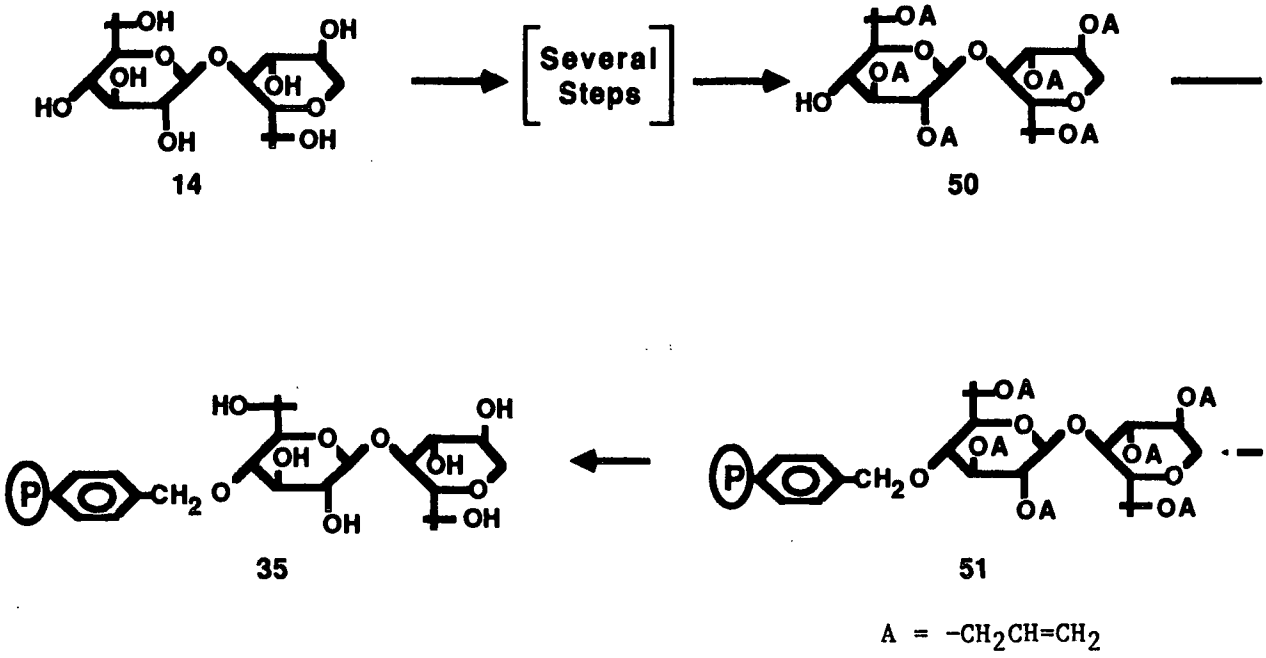


Figure 13. Protection, benzylation and deprotection of methyl α-D-glucopyranoside.

This approach (Scheme 2) to the polymer-supported model requires the preparation of an allyl protected 1,5-anhydrocellobiitol (50). The strategy was to provide an unequivocal synthesis of the supported model. The individual steps of the synthesis and the characterization of the intermediates will be described later.

Scheme 2



PREPARATION OF METHYL 4-O-BENZYL-α-D-GLUCOPYRANOSIDE

Methyl 4-O-benzyl-α-D-glucopyranoside (49) was prepared according to Fig. 14 to test the alkaline stability of the proposed benzyl ether linkage. Methyl α-D-glucopyranoside (47) was benzylidenated and acetylated to yield 52. The acetate esters present in 52 were removed catalytically with sodium methoxide to give the 4,6-O-benzylidene 53. Compound 53 was allylated to yield 54 which was debenzylidenated and selectively tosylated to give 55. The tosyl group in 55 was displaced by sodium allylate to yield the 2,3,6-tri-O-allyl derivative 56. Compound 56 was condensed with benzyl bromide to yield 57. The allyl groups in 57 were removed to give the 4-O-benzyl product 49.

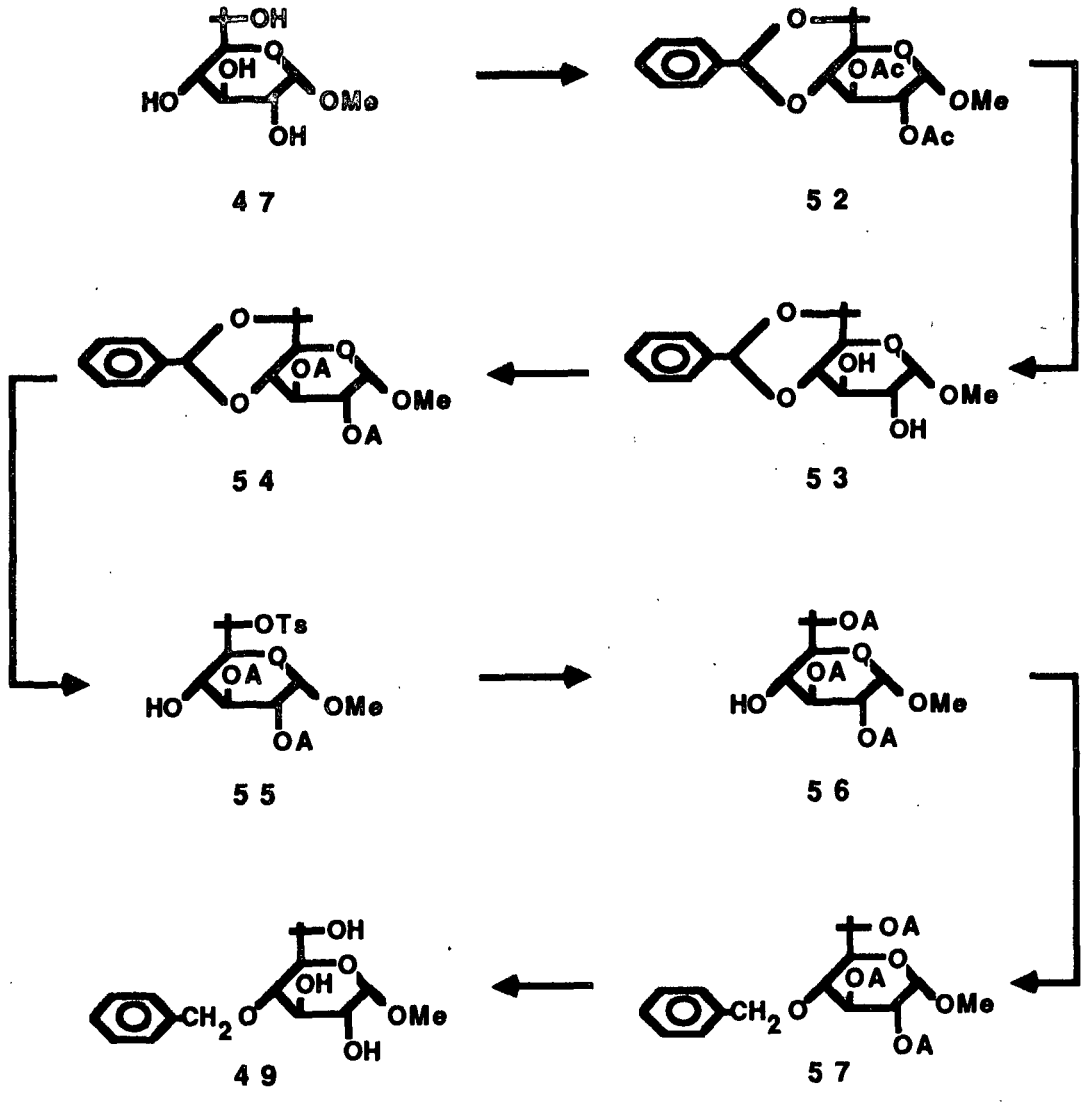


Figure 14. Synthetic scheme for the preparation of methyl 4-O-benzyl-α-D-glucopyranoside (49).

ALKALINE STABILITY OF THE BENZYL ETHER LINKAGE

Alkaline Degradation of Methyl 4-O-benzyl-α-D-glucopyranoside

The benzyl ether's resistance to alkaline cleavage was verified by degrading methyl 4-O-benzyl-α-D-glucopyranoside (49) in 2.5N sodium hydroxide at 170°C. The rate of disappearance of 49 was described by Eq. (1).

$$\frac{dR}{dt} = -k[R]^a[^-OH]^b \qquad (1)$$

where $[R]$ = reactant concentration, mol L^{-1}
$[^-OH]$ = hydroxide ion concentration, mol L^{-1}
k = rate constant for the disappearance of reactant, sec^{-1}
t = time, sec
a = constant, assumed to be 1.0
b = constant

Since hydroxide ion was present in a large excess, its concentration was assumed to be constant and Eq. (1) was written as

$$\frac{dR}{dt} = -k_r[R] \qquad (2)$$

where $k_r = k[^-OH]^b$, pseudo-first order rate constant for the disappearance of reactant.

Integration of Eq. (2) gave

$$\ln R = -k_r t + \ln R_0 \qquad (3)$$

where R_0 = initial reactant concentration, mol L^{-1}.

The pseudo-first order rate constant for the disappearance of **49** was calculated by a least squares method according to Eq. (3). The linearity of the data indicated the reaction was first order with respect to methyl 4-O-benzyl-α-D-glucopyranoside (Fig. 15).

The rate of disappearance of **49** was 1.75×10^{-7} sec^{-1} or approximately forty times slower than the rate of disappearance of 1,5-anhydrocellobiitol[16] under similar conditions. It should be pointed out that this compound may degrade by either benzyl ether cleavage or glycosidic bond cleavage. Therefore, this rate should be taken as a minimum estimate of the benzyl ether stability.

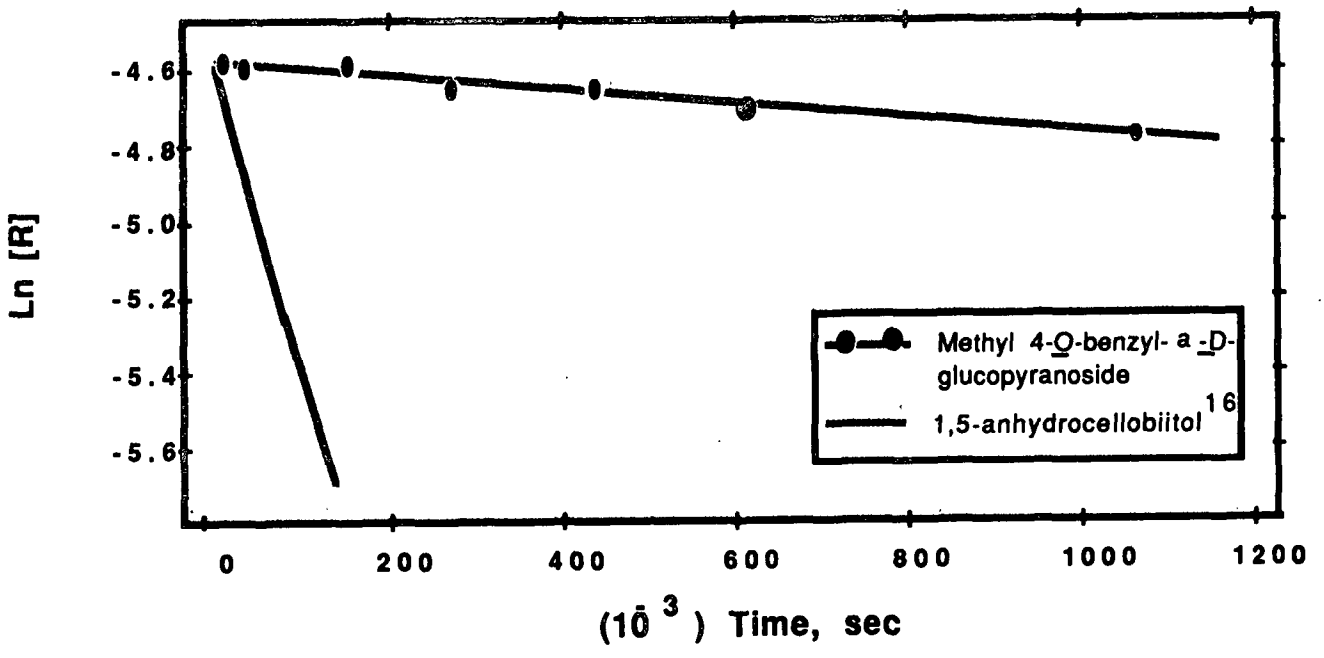


Figure 15. Degradation of methyl 4-O-benzyl-α-D-glucopyranoside (49) and 1,5-anhydrocellobiitol (14) in 2.5N sodium hydroxide at 170°C.

Benzyl-Oxygen Bond Cleavage in Methyl 4-O-benzyl-α-D-glucopyranoside

Benzyl ether cleavage in methyl 4-O-benzyl-α-D-glucopyranoside may occur at either the benzyl-oxygen bond or the oxygen-sugar bond (Fig. 16). Since Brandon[16] concluded that the oxygen-aglycon bond in 1,5-anhydrocellobiitol does not cleave by a neighboring group reaction, the most probable mechanisms for benzyl ether cleavage in 49 are S_N1 and S_N2. Also, based on the reactivity of benzylic compounds, the benzyl-oxygen bond cleavage should dominate. According to Streitwieser,[48] reaction at the benzyl carbon by either an S_N1 or an S_N2 mechanism would be expected to be at least 100 times faster than at the secondary sugar carbon (C-4) (Table 4).

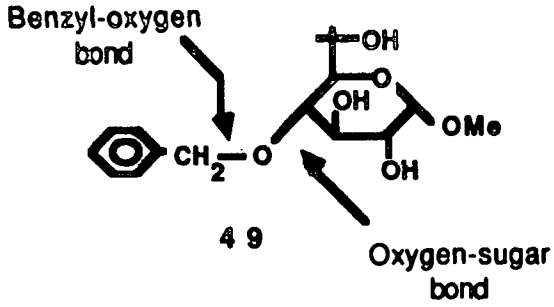
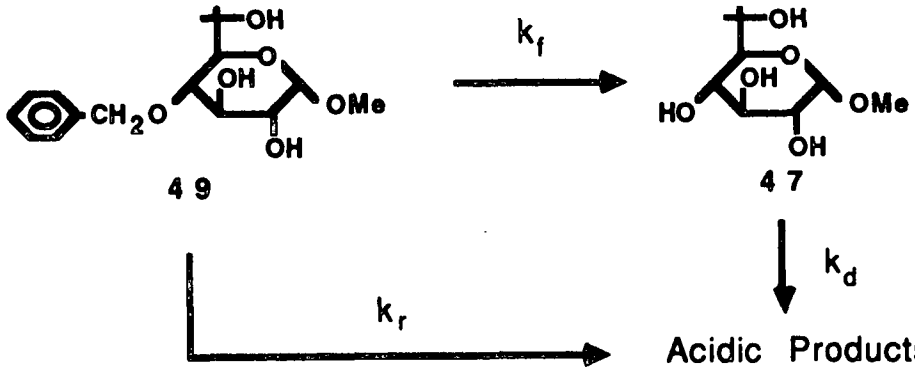


Figure 16. Benzyl-oxygen and oxygen-sugar bonds in methyl 4-O-benzyl-α-D-glucopyranoside (49).

Table 4. Relative rates between benzylic and alkyl substrates and for S_N1 and S_N2 reactions.[48]

Group	Relative Rate for S_N1	Relative Rate for S_N2
Ethyl	0.26	1.0
iso-Propyl	0.69	0.025
Benzyl	100.0	120.0

A better estimate of benzyl ether cleavage may be obtained by determining the amount of 49 which degrades by benzyl-oxygen bond cleavage. Cleavage of this bond always results in formation of methyl α-D-glucopyranoside. It may be diagrammed as follows:[16]



The fraction which degrades by benzyl-oxygen cleavage is equal to the ratio of the rate constant for the formation of methyl α-D-glucopyranoside (k_f) to the rate constant for the disappearance of methyl 4-O-benzyl-α-D-glucopyranoside (k_r).

The methyl α-D-glucopyranoside (47) is not stable under the reaction conditions, and therefore, its concentration at any time t is dependent on both its rate of formation (k_f) and disappearance (k_d). Brandon, et al.,[16] reported a mathematical expression for determining k_f of labile reaction products. The rate of change in the concentration of the intermediate can be expressed as

$$\frac{dI}{dt} = k_f[R] - k_d[I] \tag{4}$$

where [I] = intermediate concentration, mol L^{-1}.

Substitution of Eq. (3) into Eq. (4) and rearrangement yields:

$$\frac{dI}{dt} + k_d[I] = k_f[R_o]e^{-k_r t} \tag{5}$$

Equation (5) is a linear first order differential equation. Its solution requires the use of an integrating factor. Therefore, let

$$\frac{dI}{dt} + k_d[I] = 0 \tag{6}$$

Integration of Eq. (6) gives:

$$c = [I]e^{k_d t} \tag{7}$$

where c = constant

$e^{k_d t}$ = the integration factor.

Hence, multiplication of Eq. (5) by the integrating factor and integration yields:

$$[1]e^{k_d t} = \frac{k_f[R_0]}{k_d - k_r} e^{(k_d - k_r)t} + C \qquad (8)$$

On setting $[1] = [1_0]$ at $t = 0$, rearrangement gives:

$$C = [1_0] - \frac{k_f[R_0]}{k_d - k_r} \qquad (9)$$

Substitution of Eq. (9) into Eq. (8) and rearrangement yields:

$$[1] - [1_0]e^{-k_d t} = k_f \left\{\frac{[R_0]}{k_d - k_r} (e^{-k_r t} - e^{-k_d t})\right\} \qquad (10)$$

In theory a plot of the bracketed portion of the right hand side of Eq. (10) versus the left hand side yields a graph with slope k_f. The value of k_d was determined in an earlier study by Gilbert[12] to be 6.53×10^{-7} sec^{-1} at 170°C in 2.5N sodium hydroxide.

Analysis of the kinetic samples by GLC indicated that only trace amounts of methyl α-D-glucopyranoside were present at any time in the reaction. Attempts to fit this data to Eq. (10) resulted in a nonlinear curve, giving no indication of the importance of benzyl ether cleavage. The nonlinear nature of this curve may be a result of the experimental error associated with measuring the low concentrations of methyl α-D-glucopyranoside.

A series of curves for the theoretical concentration of methyl α-D-glucopyranoside may be generated by first recognizing that:[12]

$$k_f = Fk_r \qquad (11)$$

where F = fraction of methyl 4-O-benzyl-α-D-glucopyranoside which degrades to form methyl α-D-glucopyranoside

and then substituting Eq. (11) into Eq. (10) and varying the value of F (Fig. 17). A comparison of these curves to the actual experimental concentration of

methyl α-D-glucopyranoside shows that the value of k_f, rate of benzyl-oxygen bond cleavage in methyl 4-O-benzyl-α-D-glucopyranoside, is equal to 0.25 k_r or 4.4×10^{-8} sec^{-1}. Based on this, the rate of glycosidic bond cleavage in 1,5-anhydrocellobiitol (7.9×10^{-6} sec^{-1})[16] is approximately 180 times faster than the rate of benzyl-oxygen bond cleavage in methyl 4-O-benzyl-α-D-glucopyranoside. Thus, a benzyl linkage to the polymer should be sufficiently stable for use in this study.

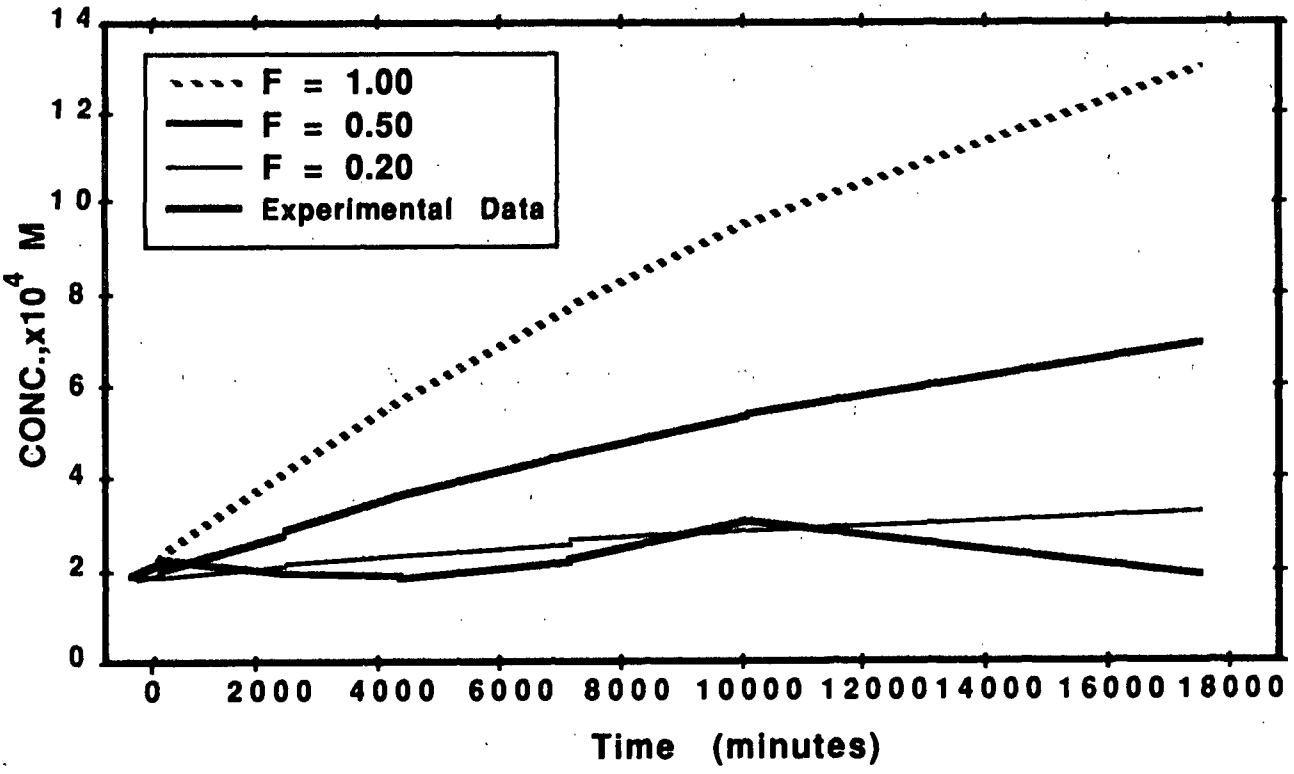
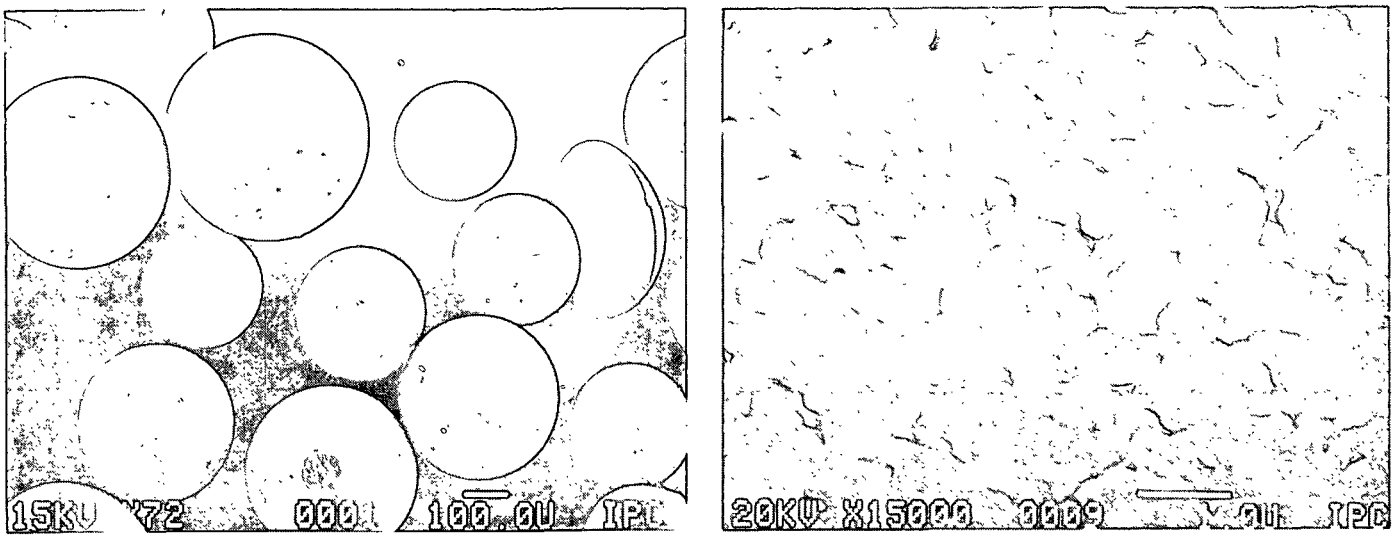


Figure 17. Correlation of the concentration of methyl α-D-glucopyranoside (47) and the time for various fractions, F, of methyl 4-O-benzyl-α-D-glucopyranoside (49) forming methyl α-D-glucopyranoside (47) at 170°C in 2.5N sodium hydroxide.[12]

ALKALINE STABILITY OF THE POLYSTYRENE RESIN

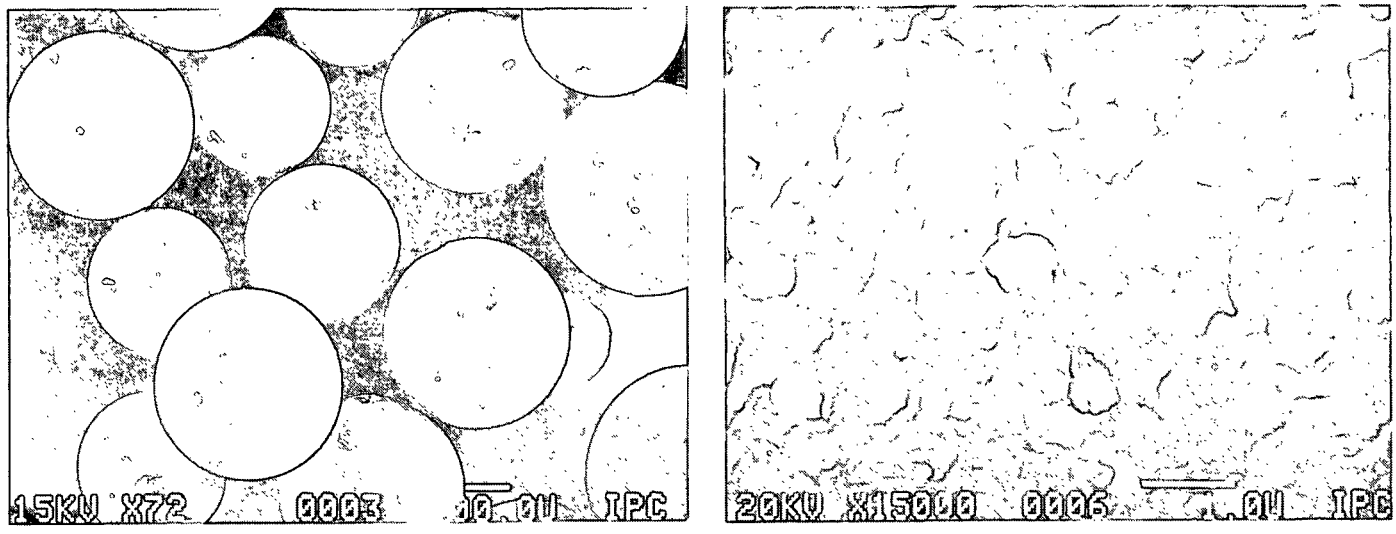
The polystyrene's resistance to high temperature alkaline attack was verified by treating the unfunctionalized resin (58) with 2.5N sodium hydroxide

at 170°C for five days. Gravimetric analysis showed no weight loss had occurred. Also the only observable microscopic differences between treated and untreated resins were minor increases in mechanical damage (Fig. 18 and 19).



a b

Figure 18. Electronmicrographs of unfunctionalized Amberlite XE-305 polystyrene: a. 15 KV x 72. b. 20 KV x 15,000.



a b

Figure 19. Electronmicrographs of unfunctionalized Amberlite XE-305 polystyrene after treatment with 2.5N sodium hydroxide at 170°C for five days: a. 15 KV x 72. b. 20 KV x 15,000.

SYNTHESIS OF THE POLYMER SUPPORTED MODEL

Functionalization of the Polymer Support

The preparation of the polymer-bound benzyl iodide (60) is outlined in Fig. 20. Amberlite XE-305 resin (58) was chloromethylated to yield resin 59. Resin 59 contained 5.03 millimoles chlorine per gram and its IR spectrum showed a strong CH_2 (wagging) absorption band at 1260 cm^{-1} (Fig. 54, Appendix III). The chloromethyl groups were converted to the more reactive iodomethyl functions by refluxing 59 with sodium iodide in acetone.[49] Displacement of the chlorine by iodine was indicated by the shift in the IR spectrum of the CH_2 absorption band to 1155 cm^{-1} in 60 (Fig. 55, Appendix III) and confirmed by elemental analysis. The iodomethylated resin (60) contained 2.78 millimoles of iodine per gram, corresponding to three iodomethyl groups per five aryl rings.

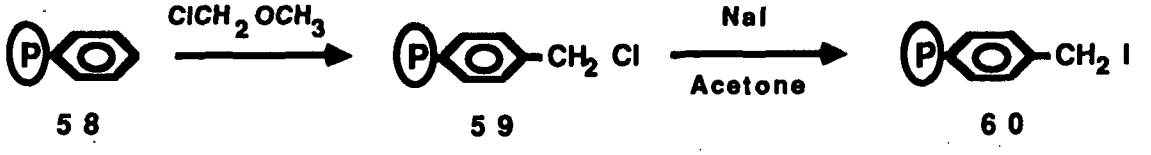


Figure 20. Preparation of the polymer-bound benzyl iodide (60).

Preparation of the Allyl Protected 1,5-Anhydrocellobiitol (50)

The allyl protected 1,5-anhydrocellobiitol (50) was prepared according to the scheme shown in Fig. 21. The first objective was the preparation of 1,5-anhydrocellobiitol (14). Syntheses of 1,5-anhydroalditols have been reviewed.[50,51] Schroeder and coworkers,[15,52] have prepared esterified 1,5-anhydroalditols by reductive desulfuration of esterified 1-thioglycopyranosides with Raney nickel and by palladium and platinum catalyzed hydrogenation of esterified glycopyranosyl halides in the presence of amines. The Raney nickel-desulfuration has been preferred for large scale preparations because of good yield and ease of isolation. In contrast large scale catalytic hydrogenations

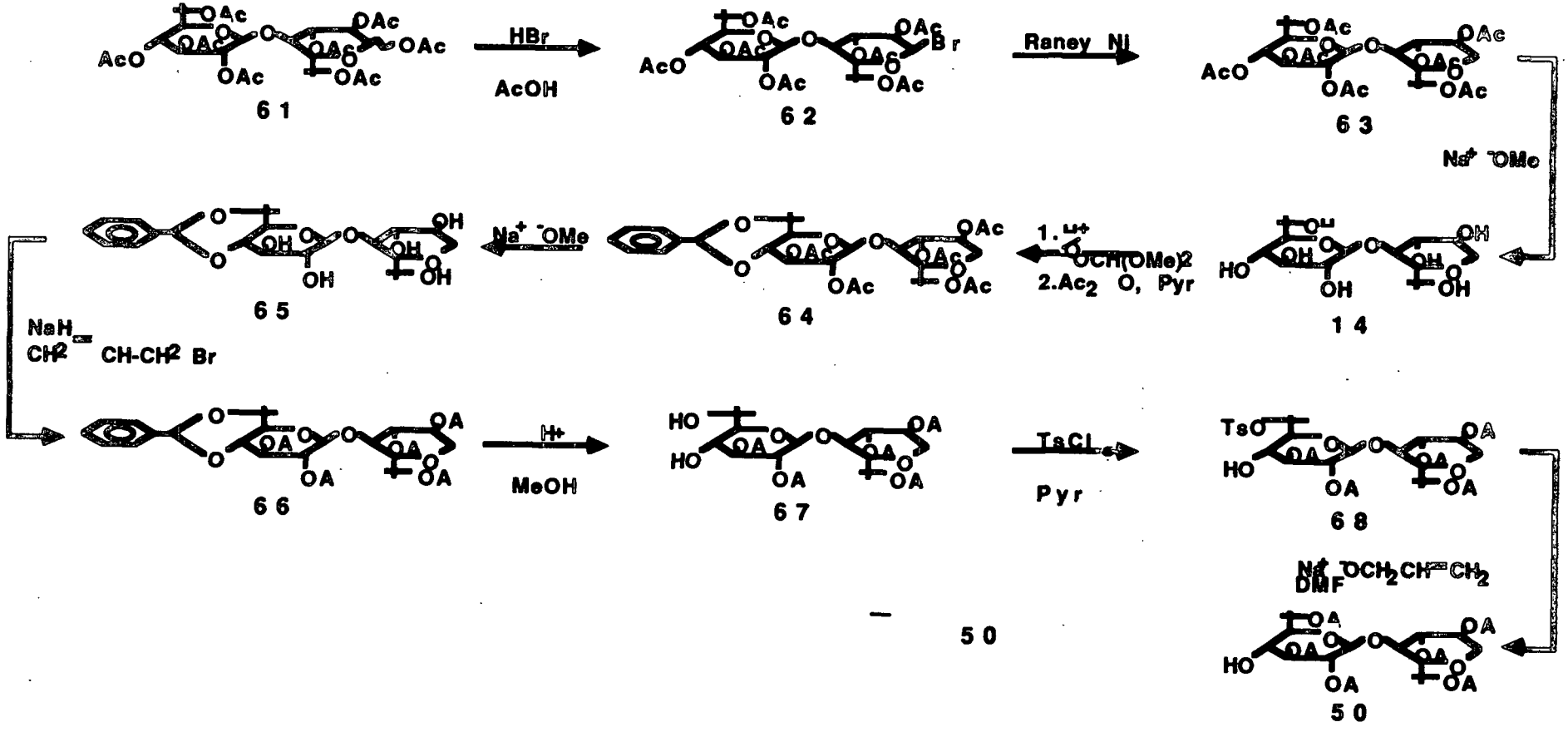


Figure 21. Synthetic scheme for the preparation of 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3,6-tri-O-allyl-β-D-glucopyranosyl)-D-glucitol (50).

have not been preferred because they result in complex product mixtures that require chromatographic purification. However, since the thioglycosides are typically synthesized from glycosyl halides, direct reduction of the glycosyl halide was investigated.

Cellobiose octaacetate (61) was treated with hydrobromic acid in glacial acetic acid to yield α-cellobiosyl bromide heptaacetate (62). Reductive dehalogenation of 62 with Raney nickel in the presence of triethylamine afforded 1,5-anhydrocellobiitol heptaacetate (63) in excellent yield (78%). The acetate esters present in 63 were removed with methanolic sodium methoxide to give 14.

The Raney nickel reduction of the glycosyl halide provided an excellent means of preparing large quantities of 63. The only report of a similar reduction is a brief mention of the reduction of tri-O-benzoyl-β-D-arabinopyranosyl bromide with Raney nickel as part of a study on the preparation of 2-deoxy sugars by hydrogenolysis of benzoylated glycopyranosyl bromides.[53] The yield of the deoxy sugars was only 3% but the yield of 1,5-anhydro-tri-O-benzoyl-D-arabinitol was 52%. Although a trace amount of the deoxy analog of 1,5-anhydrocellobiitol was detected by GLC, it did not interfere with the crystallization of 63. The physical constants of 14 were consistent with the desired product.

Differences in the reactivity of carbohydrate hydroxyl groups have been recognized for some time. Some of these differences are easily predicted. For example, classical organic chemistry predicts that the primary hydroxyl groups are much more reactive than the secondary hydroxyl groups, and indeed, this is observed. The primary hydroxyl groups can be selectively blocked with a variety of protecting groups (trityl, benzoyl, tosyl, ...) without blocking the secondary

hydroxyl groups. However, the differences in the reactivity of the individual secondary hydroxyl groups is much smaller and therefore, harder to predict.

In order to transform 1,5-anhydrocellobiitol into its hexaallyl ether (50), it was necessary to first isolate the C-4' hydroxyl group from the other secondary hydroxyl groups. Treatment of 14 with α,α-dimethoxytoluene in N,N-dimethylformamide in the presence of p-toluenesulfonic acid gave the benzylidene derivative 65. The conditions employed were essentially the same as those reported by Evans[54] for the preparation of methyl 4,6-O-benzylidene-α- and β-D-glucopyranoside. Formation of 65 was confirmed by ^{13}C-NMR spectroscopy, which indicated the presence of aromatic carbons at 136.0, 128.7, 127.8, and 125.8 ppm and two acetal carbons at 103.6 and 100.6 ppm (Fig. 30, Appendix I). Also, the El mass spectrum showed fragments corresponding to loss of the benzylidene group (265, M-149),[55] the aglycon (251, M-163), and the glycon (147, M-267) (Table 10, Appendix II).

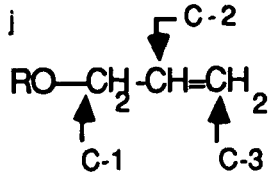
Attempts to isolate 65 directly from 14 afforded only low yields (30%). Thus, the reaction mixture from benzylidenation of 14 was acetylated in situ and the product was isolated as its per acetate 64. Compound 65 was obtained by catalytic deacetylation of 64 with sodium methoxide. The conversion of 14 → 64 → 65 increased the yield of 65 to 65%.

Next, the free hydroxyl groups in 65 were protected with allyl ethers. Etherification with allyl bromide and sodium hydride in N,N-dimethylformamide gave crystalline 66 (59%). That 66 was completely allylated was apparent from the ratio of vinylic to aromatic protons (3:1) observed in the ^{1}H-NMR spectrum (Fig. 43, Appendix I). Also, the ^{13}C-NMR spectrum of 66 showed signals at 135.2, 134.5, and 134.1 ppm for the 2-C allyl carbon and 116.6, 116.1, and 115.4 ppm for the 3-C allyl carbon (Fig. 31, Appendix I).

Removal of the benzylidene group with dilute acid and methanol gave **67**. Although direct allylation of the primary hydroxyl group in **67** is possible, it was not attempted since selective etherifications generally result in low yields.[56] Instead a new two step procedure used to etherify primary hydroxyl groups was employed.[56] This method combines a regioselective tosylation of the C-6 hydroxyl group with a subsequent nucleophilic displacement of the tosyloxyl substituent by a sodium alkoxide.

Compound **67** was not isolated. Its primary hydroxyl group was selectively tosylated to yield **68** as an amorphous sirup. Purification by column chromatography afforded a low yield (50%) of **68** and allowed the recovery of unreacted **67**. The formation of **68** was apparent from its NMR spectra. The aromatic signals in the ^{1}H-NMR were split into an AA'BB' pattern indicative of p-substituted benzene rings such as a p-tosyl group (Fig. 44, Appendix I). Also the ratio of vinylic to aromatic protons (15:4) was consistent with **68**. The ^{13}C-NMR spectrum showed signals at 21.4 ppm for the tosyl methyl carbon and 144.6 ppm for the sulfur substituted aromatic carbon (Fig. 32, Appendix I).

Treatment of **68** with sodium allylate in N,N-dimethylformamide and purification by column chromatography gave the hexaallyl ether protected disaccharide **50** as a sirup. Both the ^{1}H and ^{13}C-NMR spectra were consistent with the proposed structure of **50** (Fig. 33 and 45, Appendix I). The overall yield of **50** based on **61** was 5%.



Unfortunately, 50 can polymerize if not stored properly. A literature survey revealed that allyl ethers of complex carbohydrates such as starch and cellulose form infusable resins when exposed to air and light.[57] Therefore, preparations of 50 were immediately coupled to the polymer support or stored in the dark under nitrogen.

Preparation of the Supported 1,5-anhydrocellobiitol (35)

Condensation of 50 with the polymer-bound benzyl iodide (60) was effected in 33% yield (based on 50 consumed) by stirring a tetrahydrofuran (THF) suspension of the polymer with the glycoside and sodium hydride (Fig. 22). The IR spectrum of the product, resin 51, indicated a strong C-O absorption at 1150-1000 cm^{-1} and two moderate to weak olefinic C-H absorptions at 996 and 923 cm^{-1} (Fig. 56, Appendix III). Also treatment of 51 with ozone generated formaldehyde indicating the presence of allyl groups.

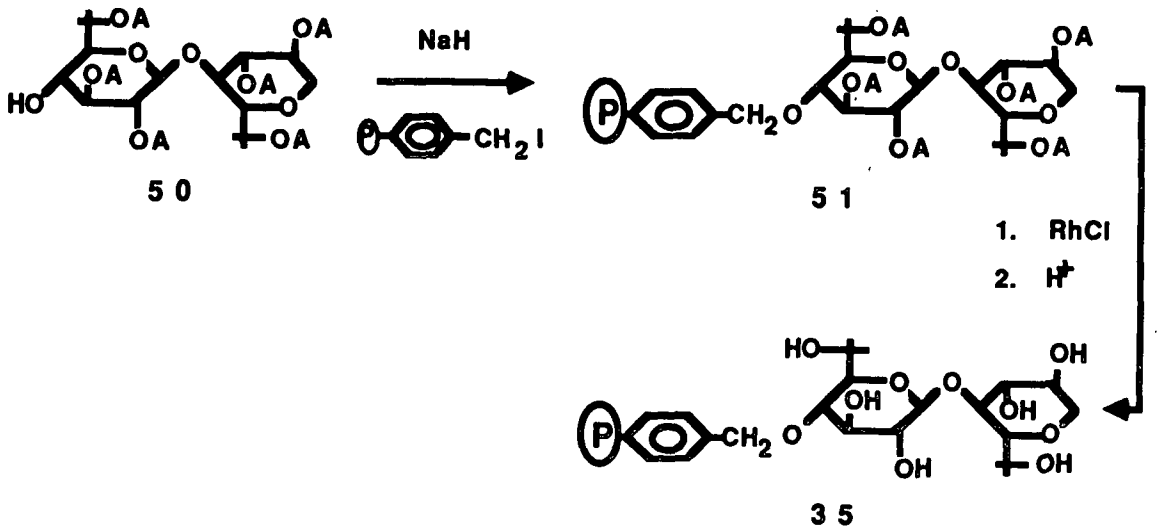


Figure 22. Preparation of the supported 1,5-anhydrocellobiitol (35).

An attempt to condense the protected disaccharide 50 with the polymer-bound benzyl iodide 60 in dimethyl sulfoxide (DMSO) resulted in little reaction. The IR spectrum of the recovered resin showed only a minor increase in the C-O absorption band (Fig. 57, Appendix III). In view of the enhanced reactivity normally obtained by using DMSO as a solvent in displacement reactions, this result was surprising.[58] However, the low level of reaction was probably due to the poorer swelling property of DMSO as compared to THF. The DMSO, being more polar than THF, does not swell the polymer matrix to as great an extent.

The unreacted benzyl iodide groups on 51 were converted to benzyl ethyl ethers by treatment with sodium ethoxide. The allyl ether protecting groups were then isomerized with tristriphenylphosphinerhodium chloride (TPRC) and removed by acid hydrolysis to give 35.[59] The removal of the allyl ethers was confirmed by the disappearance of the olefinic C-H absorptions at 996 and 923 cm^{-1} and the appearance of a broad OH absorption between 3600 and 3000 cm^{-1} in the IR spectrum of 35 (Fig. 58, Appendix III).

CHARACTERIZATION OF THE POLYMER-SUPPORTED MODEL

Loading

The loading* was determined by measuring the increase in weight of resin 51 upon treatment with osmium tetraoxide. Resin 51 contains allyl ethers which in the presence of pyridine react quantitatively with osmium tetraoxide to form osmylate esters (Fig. 23).[75] Unfortunately, osmium tetraoxide also reacts with aromatic double bonds. However, the rate of this reaction is much slower.[79] To correct for this, unfunctionalized resin (58) was also osmylated and its increase

*Loading = mmoles of reagent per gram of polystyrene.

in weight was subtracted from 51's. The loading determined by this method was 0.25 millimole of 1,5-anhydrocellobiitol per gram of 35.

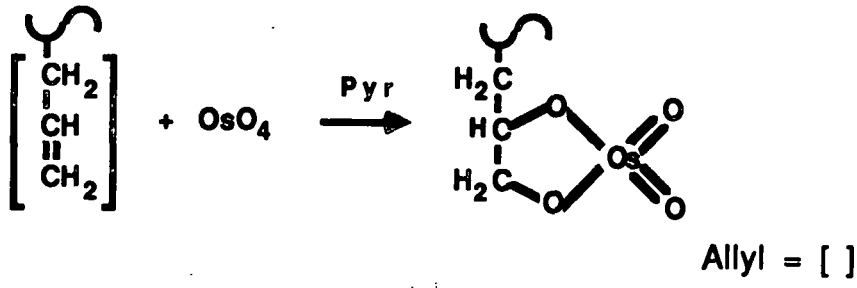


Figure 23. Osmylation of allyl ethers.

This loading was confirmed by hydrolyzing the supported disaccharide's glycosidic bond and monitoring the amount of the aglycon, 1,5-anhydro-D-glucitol, released into the liquid phase. The hydrolysis was performed in aqueous ethanol with hydrochloric acid. It was continued until the concentration of 1,5-anhydro-D-glucitol in the solution remained constant. The loading determined by this method was 0.22 millimole of 1,5-anhydrocellobiitol per gram of resin 35. Although this value is slightly lower than the value determined by the osmylation method, it is considered to be a better estimate of the loading, since the osmylation may suffer from potential side reactions.

Point of Polymer Attachment

The point by which the polymer is attached to the disaccharide may be inferred from the analogous preparation of methyl 4-O-benzyl-α-D-glucopyranoside to be the C-4' position. However, based on the last crystalline material in the synthesis, compound 66 (Fig. 21, page 38), the polymer could be attached through either the C-4' or C-6' position. In order to distinguish between these two possibilities and verify that the polymer was indeed covalently bound to the 1,5-anhydrocellobiitol, resin 35 was exhaustively methylated and the benzyl

ether linkage was cleaved by an acid hydrolysis.[76] The hydrolysis also cleaved the disaccharide's glycosidic bond. The products were analyzed by GLC and GC-MS spectroscopy as their alditol acetates.

In each case the aglycon would yield 4-O-acetyl-1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (72). However, the product from the glycon would be dependent on the point of attachment (Fig. 24). The glycon from the C-6' bound disaccharide would yield 1,5,6-tri-O-acetyl-2,3,4-tri-O-methyl-D-glucitol (69) and the C-4' bound disaccharide would yield 1,4,5-tri-O-acetyl-2,3,6-tri-O-methyl-D-glucitol (70). Any nonbonded disaccharide would yield 1,5-di-O-acetyl-2,3,4,6-tetra-O-methyl-D-glucitol (71).

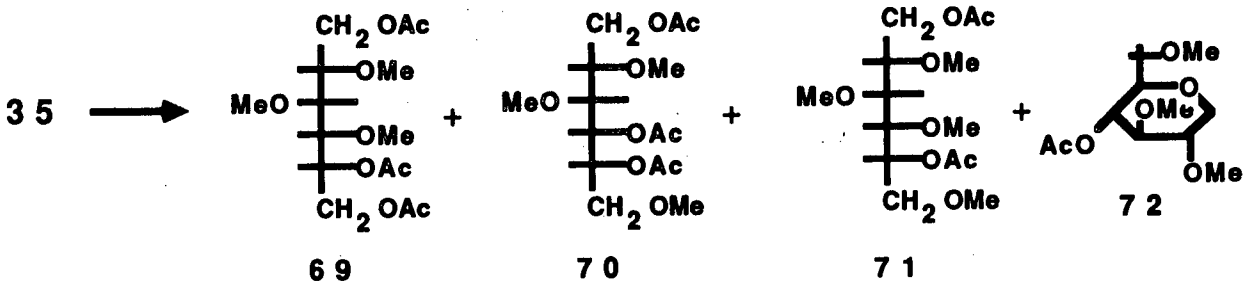


Figure 24. Potential products from methylation and hydrolysis of polymer-supported 1,5-anhydrocellobiitol (35).

The GLC and GC-MS analyses of the methylation-hydrolysis products showed approximately equal amounts of 4-O-acetyl-1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (72) and 1,4,5-tri-O-acetyl-2,3,6-tri-O-methyl-D-glucitol (70). Neither 69 or 71 was detected in the reaction mixture. The presence of 70 and the absence of 69 and 71 confirms that the polymer was covalently bound through the disaccharide's C-4' position.

Distribution

The distribution of the disaccharide across the polymer support was determined by electron microscopy. Resin 51 was osmylated, cross sectioned, and mapped for osmium. The concentration of osmium and therefore the disaccharide was greatest at the outer surfaces and least in the center (Fig. 25).

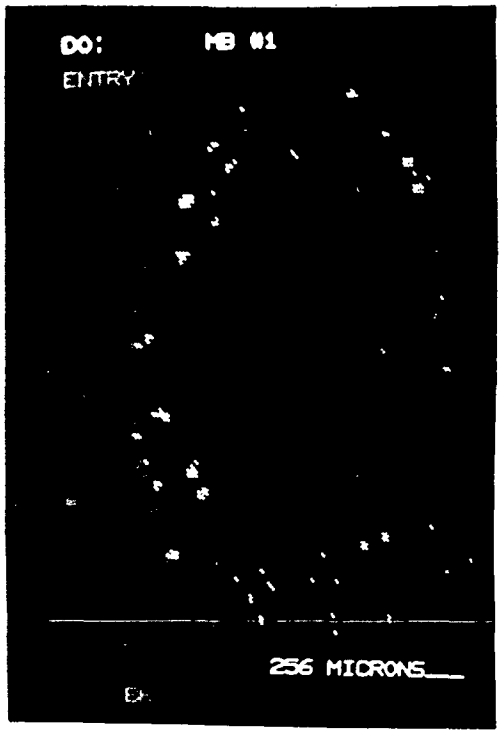


Figure 25. Osmium distribution in resin 51 - cross section was carbon coated prior to analysis. Osmium concentration: blue > red > black.

Caution must be used in interpreting these results. The initial analyses were plagued by intense internal reflectance of the microscope's x-ray beam (Fig. 26). To combat this, the cross sectioned resins were carbon coated prior to analysis. Although this eliminated the reflectance problem, it also reduced the microscope's sensitivity. Thus, the inability to detect osmium on the internal surfaces should be taken only as an indication of lower concentration and not the total absence of osmium.

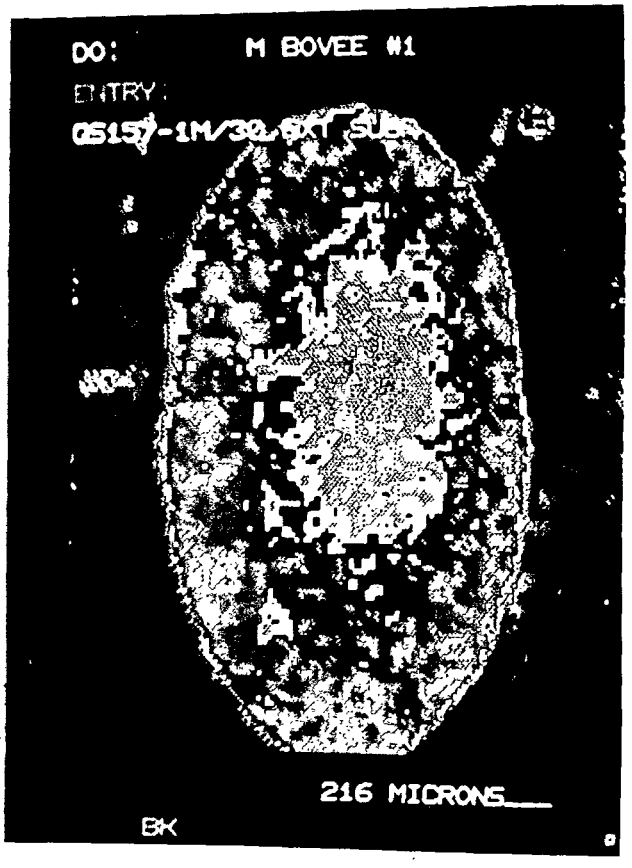


Figure 26. Osmium distribution in resin 51 prior to carbon coating. Osmium concentration: white > blue > red > black.

CONCLUSIONS

The preparation and characterization of a solid-supported cellulose model was accomplished. The model consists of a 1,5-anhydrocellobiitol unit attached through its C-4' position to a polystyrene resin by a benzyl ether bond. The model loading was 0.22 millimole of 1,5-anhydrocellobiitol per gram of polystyrene resin. The distribution of the disaccharide throughout the support was not uniform. The concentration of 1,5-anhydrocellobiitol was greatest at the outer surfaces of the support.

The synthetic scheme employed in the preparation of the supported model was also used to synthesize methyl 4-O-benzyl-α-D-glucopyranoside. The scheme is a general method for the synthesis of 4-O-alkyl substituted hexoses. This synthetic scheme can be readily adapted to the preparation of a variety of supported cellulose models.

The benzyl ether linkage and the polystyrene resin should be sufficiently stable for use in alkaline degradation studies. The rate of glycosidic bond cleavage in 1,5-anhydrocellobiitol[16] at 170°C in 2.5N sodium hydroxide was at least 180 times faster than the rate of benzyl-oxygen bond cleavage in methyl 4-O-benzyl-α-D-glucopyranoside under similar conditions. Only minor mechanical damage was observed upon treatment of the unfunctionalized polystyrene with 2.5N sodium hydroxide at 170°C.

The supported model developed in this work should provide a new tool for studying glycosidic bond cleavage. The model's insolubility should allow the investigator to gain new insight on glycosidic bond cleavage in cellulose.

EXPERIMENTAL

GENERAL

Melting points were determined on a calibrated Thomas-Hoover capillary apparatus. Optical rotations were obtained with a Perkin-Elmer 141MC polarimeter. The NMR spectra were determined with a JEOL FX100 Fourier transform spectrometer at normal probe temperature using TMS as an external standard. The IR spectra were obtained as KBr pellets with a Nicolet 7199 Fourier transform spectrometer. Electron micrographs were obtained with a JEOL 35C electron microscope.

Thin layer chromatography (TLC) was performed on microscope slides coated with silica gel G (Merck Kieselgel D-5). The solvents for development are described in the appropriate sections. Components were detected by spraying the chromatography with H_2SO_4 in MeOH (1:4 v/v), followed by charring.

Gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 5890 instrument equipped with a flame ionization detector and interfaced with a Hewlett-Packard 3392A integrator. Helium was used as the carrier gas at a rate of 25 mL/min. The following columns and operating conditions were used:

(A) OV-17 (3%) on Supelcoport (80-100 mesh) in a glass column (6 ft x 1/4-inch x 2 mm). The operating conditions were: injector, 275°C; detector, 300°C; and column, 190°C for 20 minutes, 10°/minute to 275°C, and held at 275°C.

(B) OV-17 (3%) on Supelcoport (80-100 mesh) in a glass column (6 ft x 1/4-inch x 2 mm). The operating conditions were:

injector, 275°C; detector, 300°C; and column, 170°C for 15 minutes, 10°/minute to 220°C, and held at 220°C.

(C) SP-2340 on Supelcoport (80-100 mesh) in a glass column (6 ft x 1/4-inch x 2 mm). The operating conditions were: injector, 200°C; detector, 225°C; and column, 170°C for 40 minutes.

(D) OV-17 (3%) on Supelcoport (80-100 mesh) in a glass column (6 ft x 1/4-inch x 2 mm). The operating conditions were: injector, 275°C; detector, 300°C; and column, 210°C for 20 minutes, 5°/minute to 250°C and held at 250°C.

Table 5 gives response factors and retention times for the GLC analyses.

Table 5. Gas chromatographic retention times (T_r) and response factors (F_x).

Conditions	Compound	T_r, min	F_x
A	1,5-Anhydro-D-glucitol (21)	5.80	0.846[a]
A	D-Glucitol (73)	16.51	1.000[a]
B	4-O-acetyl-1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (72)	2.38	--
B	1,4,5-Tri-O-acetyl-2,3,6-tri-O-methyl-D-glucitol (70)	12.69	--
C	1,5,6-Tri-O-acetyl-2,3,4-tri-O-methyl-D-glucitol (69)	28.70	--
C	1,4,5-Tri-O-acetyl-2,3,6-tri-O-methyl-D-glucitol (70)	31.49	--
D	Methyl α-D-glucopyranoside (47)	3.50	0.803[b]
D	Methyl-4-O-benzyl-α-D-glucopyranoside (49)	23.70	1.173[b]
D	2-Hydroxyethyl 1-thio-β-D-glucopyranoside (74)	25.40	1.000[b]

[a]As the acetate derivative, calculated relative to D-glucitol.
[b]As the acetate derivative, calculated relative to 2-hydroxyethyl 1-thio-β-D-glucopyranoside.

Quantitative GLC utilized internal standards. Molar response factors were calculated according to Eq. (12).

$$F_x = A_r M_r \tag{12}$$

where F_x = response factor for compound x

A_r = peak area ratio of compound x to the internal standard

M_r = mole ratio of the internal standard to the compound x

A Hewlett-Packard 5985 instrument was used for direct insertion (DI) and GLC mass spectroscopy (GC/MS). The GLC conditions were similar to those described above. The GC/MS interface was maintained at 250°C. Electron impact (EI) MS used helium as the carrier gas, a source temperature of 200°C, and an ionization voltage of 70 Ev.

Ozone was generated with a Welsbach T-816 apparatus from industrial oxygen. The oxygen supply was dried by passage through drierite. The operating conditions were: gas inlet pressure, 8 psig; potential, 75 V; and current, 70 W. The ozone/sample stream split was 0.5/3.0.

SOLVENTS, REAGENTS, AND CATALYST

Acetic Anhydride

Reagent grade acetic anhydride (1 L) was fractionally distilled. The first 100 mL were discarded, and the next 700 mL were collected and stored in dark bottles.

Anhydrous Methyl Alcohol

A solution of magnesium turnings (10 g), iodine (0.5 g), and methanol (50 mL) was warmed until the iodide disappeared and all the magnesium turnings were

converted to magnesium oxide.[60] Reagent grade methanol (1.5 L) was added, refluxed for two hours and fractionally distilled. The first 250 mL were discarded and the next 1000 mL were collected.

Anhydrous Pyridine

Reagent grade pyridine (1 L) was refluxed over potassium hydroxide pellets (400 g) for four hours and fractionally distilled.[60] The first 250 mL were discarded, and the next 1000 mL were collected and stored under nitrogen in dark bottles.

Benzyl Bromide

Reagent grade benzyl bromide (50 mL) obtained from Aldrich was fractionally distilled under vacuum. The first 10 mL were discarded and the next 20 mL were collected (b.p. 45-48°C, 0.6 mm Hg).

Dry N,N-dimethylformamide

Water was removed from reagent grade N,N-dimethylformamide (1.25 L) by azetropic distillation with benzene.[61] The benzene was removed by fractional distillation at atmosphere pressure. The N,N-dimethylformamide was cooled to room temperature, shaken with barium oxide, decanted, and distilled under reduced pressure (2 mm Hg). The first 150 mL were discarded and the next 900 mL were collected and stored under nitrogen over molecular sieves (Davidson, 4 Å).

α,α-Dimethoxytoluene

A solution of benzaldehyde (37.5 g), trimethylorthoformate (57.0 g), and methanol (49.0 g) containing ammonium chloride (0.75 g) was allowed to stand at room temperature until infrared analysis could not detect the presence of benzaldehyde.[62] The reaction mixture was diluted with anhydrous ether (100 mL),

filtered, washed with aqueous ammonium hydroxide and ice water (50 mL), dried over potassium carbonate, and concentrated under vacuum (43.0 g, 80%).

^{1}H-NMR data: δ 7.4-7.3 (m, 5H, aromatic), 5.39 (s, 1H, benzylic), and 3.32 (s, 6H, methoxyl).

Dimethyl Sulfoxide

Reagent grade dimethyl sulfoxide (750 mL) was distilled from crushed calcium hydroxide (14.3 g) under reduced pressure (10 mm Hg).[63] The first 100 mL were discarded, and the next 500 mL were collected and stored over molecular sieves (Davidson, 4 Å) under a nitrogen atmosphere.

Hydrogen Bromide in Acetic Acid

Hydrogen bromide gas was bubbled through a known amount of glacial acetic acid in tared 1 L reagent bottles.[15] When the solution reached about 20% (w/w) hydrogen bromide, the bottles were placed in an ice bath. The addition was terminated at 42-44% hydrogen bromide. The bottles were sealed, wrapped in aluminum foil, and refrigerated.

Methylsulfinyl Carbanion

Powdered sodium hydride (1.29 g) and freshly distilled dimethyl sulfoxide (50 mL) were combined under a nitrogen atmosphere.[64] The slurry was stirred at 70°C until the solution became clear and the evolution of hydrogen ceased (10 hours). An aliquot (1 mL) of the solution was diluted with water and titrated with hydrochloric acid (0.1N) to determine the concentration of the carbanion.

Raney Nickel Catalysis, W-5

Nickel-aluminum alloy (50/50, 200 g) was added to a stirred sodium hydroxide solution (6.4M, 1040 mL) at such a rate that the temperature of the solution

remained between 48 and 52°C.[65] The slurry was held at 50°C for one hour. The solids were washed with distilled water by decantation (3 x 1 L) and in a solid-liquid continuous extractor until the effluent was neutral. The washed nickel was solvent exchanged with tetrahydrofuran by decantation (3 x 200 mL) and by centrifugation and decantation (3 x 200 mL).

Sodium Allylate

Powdered sodium hydride (1.0 g), allyl alcohol (40 mL), and dry N,N-dimethylformamide (40 mL) were stirred for thirty minutes at room temperature under a nitrogen atmosphere. An aliquot (1 mL) of the solution was diluted with water and titrated with hydrochloric acid to determine the concentration of sodium allylate.

Sodium Methoxide

Sodium metal (6.9 g) was cut into small pieces, rinsed in hexane, slowly dissolved in anhydrous methanol (1 L), cooled to room temperature, and stored in sealed dark bottles under nitrogen.

Tetrahydrofuran

Tetrahydrofuran distilled from lithium aluminum hydride was obtained from H. Lingnowski.[60]

p-Toluenesulfonyl Chloride

Reagent grade p-toluenesulfonyl chloride (100 g) was dissolved in chloroform (150 mL), decolorized with Darco activated charcoal, and diluted with petroleum ether (350 mL, 60-90°C).[60] The solution was concentrated on a steam cone to 250 mL and crystallized by cooling in an ice-water bath: m.p. 68-70°C. Literature 69°C.[60]

Triphenylmethyl Chloride

Acetyl chloride was added to a solution of reagent triphenylmethyl chloride in chloroform. Petroleum ether was added until the solution became cloudy.[66] The product crystallized on refrigeration.

PURIFICATION AND FUNCTIONALIZATION OF THE POLYMER SUPPORT

Polystyrene (58)

Commercial Amberlite XE-305 polystyrene resin (150 g) was refluxed for thirty minutes in each of the following solvents: benzene (1.5 L), methanol (1.5 L), N,N-dimethylformamide (1.5 L), dioxane-2N aqueous sodium hydroxide (1:1 vol., 1.5 L), dioxane-2N aqueous hydrochloric acid (1:1 vol., 1.5 L), and water (1.5 L).[67] The resin was solvent exchanged between refluxing steps by decantation with the next solvent. After the final water wash the resin was extracted in a Soxhlet apparatus for four hours with diethyl ether and for twelve hours with hexane.

Chloromethylated Polystyrene (59)

A solution prepared by cautiously adding anhydrous stannic chloride (4 mL) to cold carbon tetrachloride (10 mL) and chloromethylmethyl ether (10 mL) was added dropwise with gentle stirring over a forty-five minute period to a suspension of Amberlite-305 resin (10.4 g) in carbon tetrachloride (75 mL) and chloromethylmethyl ether (12 mL).[19] The mixture was stirred at room temperature under a nitrogen atmosphere for 24 hours. The resin was isolated by filtration and washed with dioxane-water (1:1 vol., 400 mL), dioxane (2 x 400 mL), dioxane-2N hydrochloric acid (1:1 vol., 40 mL), water (2 x 400 mL), dioxane (2 x 400 mL), and tetrahydrofuran (2 x 400 mL). The resin was then extracted in a Soxhlet apparatus for 24 hours with tetrahydrofuran, six hours with diethyl ether, and

six hours with hexane. The product was dried under reduced pressure at 40°C: yield 13.79 g (~ 70% functionalization). The IR spectrum (Fig. 54, Appendix III) showed an absorbance corresponding to CH_2 wag of a chloromethyl group at 1260 cm^{-1} (7.94 μm).

Anal. Carbon, 74.08; Hydrogen, 6.41; Chloride, 17.83.

Iodomethylated Polystyrene (60)

A solution of sodium iodide (10.6 g) in acetone (50 mL) was added to a suspension of chloromethylated polystyrene (7.0 g) in acetone (250 mL).[49] The slurry was stirred overnight at reflux. The reaction mixture was cooled and filtered. The polymer beads were washed with acetone (300 mL) and hexane (2 x 200 mL), extracted in a Soxhlet apparatus with hexane for twelve hours, and dried in a vacuum oven at 40°C: yield 10.0 g. The IR spectrum (Fig. 55, Appendix III) indicated a shift in the CH_2 wag to 1155 cm^{-1} (8.66 μm) corresponding to an iodomethyl group. The loading, based on the elemental analysis corresponds to three iodomethyl groups per five aryl rings.

Anal. Carbon, 44.18; Hydrogen, 3.81; Chloride, 9.64; Iodide, 35.27.

SYNTHESIS OF COMPOUNDS

2,3,6-Tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-glucopyranosyl Bromide (62)

Cellobiose octaacetate (61) (102 g) was dissolved in 1,2-dichloroethane (460 mL) and added to a solution of hydrogen bromide in glacial acetic acid (33% wt., 100 mL).[15] The reaction was allowed to stand at room temperature for three hours. The solution was diluted with chloroform (800 mL) and poured into ice-water (1 L). The chloroform and ice water mixture was stirred for 30 minutes and separated. The chloroform phase was washed with water (1 L), saturated

aqueous sodium bicarbonate (until neutral), and water (2 x 1 L). The chloroform was dried over potassium carbonate and concentrated *in vacuo* to a crystalline residue. Recrystallization from ethyl ether-low boiling petroleum ether (80:5 vol.) yielded **62** (90.4 g, 85%): m.p. 178°C (decomp.), $[\alpha]_D$ + 96.2° (*c* 1.0, $CHCl_3$). Literature m.p. 180°C (decomp.), $[\alpha]_D$ + 96.3° (*c* 7.3, $CHCl_3$).[68]

Phenyl 2,3,6-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (75)

A solution of **62** (88 g) in chloroform (350 mL) was refluxed with methanolic potassium hydroxide (0.5M, 480 mL) containing thiophenol (30 mL).[69] The reaction was monitored by TLC ($CHCl_3$-EtOAc, 1:1 vol.). Residual bromide was hydrolyzed with silver nitrate (3%) in aqueous acetone (19:1, vol.) prior to analysis. On completion, the reaction solution was washed with distilled water (500 mL) and aqueous sodium hydroxide (2.5N, 3 x 400 mL); dried over potassium carbonate; and concentrated under reduced pressure. Crystallization from absolute ethanol gave **75** (59.4 g, 65.8%): m.p. 222.5-223.5°C $[\alpha]_D$ - 28.2° (*c* 1.29, $CHCl_3$). Literature: m.p. 225-226°C, $[\alpha]_D$ - 28.7° (*c* 1.5, $CHCL_3$).[69]

2,3,6-Tri-O-acetyl-1,5-anhydro-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-D-glucitol (63)

Hepta-O-acetyl-α-cellobiosyl bromide (**62**) (121 g) and triethylamine (10 mL) were dissolved in tetrahydrofuran (800 mL) and added to a slurry of Raney nickel (180 g) in tetrahydrofuran-ethanol (350 mL, 1:1, vol.). The mixture was stirred at 30°C for 30 minutes and then overnight at room temperature. The slurry was filtered and the catalyst was rinsed with tetrahydrofuran-ethanol. The filtrates were combined and concentrated *in vacuo* to a solid which on crystallization from absolute ethanol yielded **63** (83.5 g, 78%), m.p. 194.5-195.0°C, $[\alpha]_D$ + 3.8° ($CHCl_3$). Literature: m.p. 193.5-194.0°C, $[\alpha]_D$ + 4.1 ($CHCl_3$).[16]

Compound 63 was also prepared by reduction of phenyl hepta-O-acetyl-1-thio-β-cellobioside (75) (63 g) in tetrahydrofuran (250 mL) with Raney nickel (75 g).[15] The slurry was stirred at 48°C for three hours, cooled to room temperature, and filtered. The filtrate was concentrated under reduced pressure to a sirup. Crystallization from absolute ethanol gave 63: m.p. 193.8-194.8°C, $[\alpha]_D$ + 3.9° ($CHCl_3$). Literature: m.p. 193.5-194.0°C, $[\alpha]_D$ + 4.1 ($CHCl_3$).[16]

1,5-Anhydro-4-O-β-D-glucopyranosyl-D-glucitol (14)

Compound 63 (56 g) was dissolved in chloroform (250 mL) and deacetylated at room temperature with sodium methoxide (0.02N, 400 mL). The reaction was monitored by TLC (chloroform:ethyl acetate, 1:1, vol.). After 1 hour, the solution was neutralized with ion exchange resin (Dowex-2, H^+, 5 g) and filtered. The resin was washed with methanol (100 mL). The filtrates were combined and concentrated under reduced pressure to a sirup. Crystallization from 95% ethanol gave 14 (22 g, 78%): m.p. 203-205°C, $[\alpha]_D$ + 28.0° (c 1.0, H_2O). Literature: m.p. 204.5-205.5°C, $[\alpha]_D$ + 28.2° (c 1.5, H_2O).[16]

2,3,6-Tri-O-acetyl-1,5-anhydro-4-O-(2,3-di-O-acetyl-4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (64)

Compound 14 (4.8 g), α,α-dimethoxytoluene (2.5 g), and p-toluenesulfonic acid (0.2 g) were dissolved in dry N,N-dimethylformamide.[54] The mixture was heated to 60°C under reduced pressure (75 mm Hg) on a Buchi rotatory evaporator for four hours. The reaction solution was then cooled to room temperature, neutralized with pyridine (10 mL) and concentrated in vacuo to a sirup.

The sirup was redissolved in pyridine (60 mL) and cooled at 0°C while acetic anhydride (20 mL) was added. The reaction solution was allowed to come to room temperature, stirred for 24 hours, and poured into ice-water (500 mL). The ice-water was extracted with chloroform (2 x 200 mL) and the chloroform extracts

were washed with water (5 x 500 mL), dried over potassium carbonate, and concentrated to a sirup. A fraction of the sirup was purified by column chromatography (Merck Kieselgel 60, 70-230 mesh; eluent petroleum ether (30-60°C)-acetone, 10:3, vol.) and used as seed crystal. Crystallization from isopropyl alcohol-pyridine (50:1, vol.) gave **64** (5.3 g, 73%): m.p. 222-225°C, $[\alpha]_D$ - 15.8° (c 1.107, $CHCl_3$).

Anal. Calc. for $C_{29}H_{35}O_{15}$: Carbon, 55.86; Hydrogen, 5.65. Found: Carbon, 55.63; Hydrogen, 5.93.

MS (E1): m/e 624 (M^+), 475 (M-149), 335 (glycone), and 273 (aglycone) (Table 9, Appendix II).

^{1}H-NMR data ($CDCl_3$): δ 1.80-2.10 (15 H, m, $-COCH_3$); 5.44 [1 H, s, $ArCH(OR)_2$]; 7.00-7.50 (5 H, m, C_6H_5-) (Fig. 41, Appendix I).

^{13}C-NMR data ($CDCl_3$): ppm 19.3, 20.5, 20.6, 20.7, 20.9 ($-COCH_3$); 61.8, 66.0, 66.8, 68.2, 71.6, 72.3, 73.6, 75.5, 75.9, 76.8, 78.2, 81.3 (C-2', C-3', C-4', C-5', C-6', C-1, C-2, C-3, C-4, C-5, C-6, $CDCl_3$); 101.2 [$ArCH(OR)_2$ and C-1']; 125.7, 127.8, 128.8 (aryl); 136.1 (C-1 aryl); 168.8, 169.0, 169.4, 169.6, 169.8 ($-COCH_3$) (Fig. 29, Appendix I).

1,5-Anhydro-4-O-(4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (**65**)

Compound **64** (11.4 g) was deacetylated with sodium methoxide (1.0N, 2.5 mL) in anhydrous methanol (400 mL) and chloroform (250 mL) at room temperature. After 1 hour, the solution was concentrated in vacuo to a sirup. Crystallization from isopropyl alcohol-pyridine (50:1, vol.) gave **65** (4.4 g, 58%): m.p. 95-115°C, $[\alpha]_D$ + 3.10° (c 0.803, N,N-dimethylformamide).

Anal. Calc. for $C_{19}H_{26}O_{10}$: Carbon, 55.06; Hydrogen, 6.34. Found: Carbon, 54.71; Hydrogen, 6.35.

MS (El): m/e 265 (M-149), 251 (glycone), and 147 (aglycone) (Table 10, Appendix II).

^{1}H-NMR data (CD_3SOCD_3): δ 5.66 [1 H, s, C_6H_6 $CH(OR)_2$]; 7.00-7.50 (5 H, m, C_6H_5) (Fig. 42, Appendix I).

^{13}C-NMR data (CD_3SOCD_3): ppm 60.4, 65.9, 67.6, 69.2, 69.7, 72.7, 74.3, 76.2, 79.4, 80.2 (C-2', C-3', C-4', C-5', C-6', C-1, C-2, C-3, C-4, C-5, C-6); 100.5, 100.6 [$ArCH(OR)_2$]; 103.0 (C-1'); 126.1, 127.7, 128.7 (aryl C); 137.4 (C-1 aryl) (Fig. 30, Appendix I).

2,3,6-Tri-O-allyl-1,5-anhydro-4-O-(2,3-di-O-allyl-4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (66)

Powdered sodium hydride (6.2 g, 2.5 eq) was added to a solution of 65 (8.6 g) in dry N,N-dimethylformamide (200 mL) under a nitrogen atmosphere.[70] The suspension was stirred for fifteen minutes at 0°C before the dropwise addition of allyl bromide (15 mL). The reaction was then stirred overnight at room temperature. Dry methanol was added until effervescence ceased. The reaction solution was then diluted with chloroform (500 mL) and pyridine (10 mL), washed with water (5 x 500 mL), dried over anhydrous potassium carbonate, and evaporated under reduced pressure. Crystallization from isopropyl alcohol-pyridine (50:1, vol.) gave 66 (7.5 g, 59%): m.p. 118-119°C, $[\alpha]_D$ + 4.23 (c 0.763, $CHCl_3$).

MS (El): m/e 331 (glycone) and 267 (aglycone) (Table 11, Appendix II).

^{1}H-NMR data (CCl_4): δ 5.00-5.40 (10 H, m, $-CH_2-CH=CH_2$); 5.52 [1 H, s, $ArCH(OR)_2$]; 5.60-6.10 (5 H, m, $-CH_2-CH=CH_2$); 7.30-7.70 (5 H, m, C_6H_5-) (Fig. 43, Appendix I).

^{13}C-NMR data ($CDCl_3$): ppm 65.5, 68.0, 68.6, 71.8, 72.0, 73.4, 73.6, 73.8, 77.0, 77.4, 79.1, 80.6, 81.2, 81.6, 83.8 (C-2', C-3', C-4', C-5', C-6', C-1, C-2, C-3, C-4, C-5, C-6 and $-\underline{C}H_2-CH=CH_2$); 100.6, 100.7 [$Ar\underline{C}H(OR)_2$]; 102.8 (d, C-1') 115.4, 116.1, 116.6 (t, $-CH_2-CH=\underline{C}H_2$); 125.1, 127.4m 128.0 (d, aryl); 134.1, 134.5, 135.2 (d, $-CH_2-\underline{C}H=CH_2$); 136.9 (s, C-1 aryl) (Fig. 31, Appendix I).

2,3,6-Tri-O-allyl-1,5-anhydro-4-O-(2,3-di-O-allyl-6-O-tosyl-β-D-glucopyranosyl)-D-glucitol (68)

Compound 66 (5.8 g), reagent methanol (150 mL), and hydrochloric acid (1N, 4 mL) were combined and refluxed until TLC (silica, ethyl acetate) could not detect the presence of starting material, approximately one hour. The solution was cooled to room temperature, neutralized with pyridine (20 mL), concentrated under reduced pressure, and purified by column chromatography (Merck Kieselgel 60, 70-230 mesh; 2.5 x 50 cm; eluent chloroform-ethyl acetate, 10:1, vol.) to yield a sirup (4.9 g).

The sirup (4.0 g) was dissolved in anhydrous pyridine (150 mL), cooled to 0°C, and vigorously stirred while a solution of p-toluenesulfonyl chloride (2.2 g, 1.5 eq) in pyridine (50 mL) was added.[56] The reaction solution was allowed to come to room temperature, stirred for 24 hours, diluted with chloroform (200 mL), and poured into ice-water (200 mL). The chloroform and ice-water mixture was stirred for twenty minutes and separated. The chloroform phase was extracted with dilute acid (1.0N HCl, 5 x 200 mL), washed with water (2 x 200 mL), dried over potassium carbonate, and concentrated in vacuo to a sirup. Column chromatography (Merck Kieselgel 60, 70-230 mesh; 2.5 x 80 cm; eluent chloroform-ethyl acetate, 10:1, vol.) gave 68 (3.0 g, 56%) as a sirup.

^{1}H-NMR data ($CDCl_3$): δ 2.43 (3 H, s, $\underline{CH_3}C_6H_4SO_3$-); 5.00-5.30 (m, $-CH_2-CH=\underline{CH_2}$); 5.50-6.10 (5 H, m, $-CH_2-\underline{CH}=CH_2$); 7.32 (2 H, d, J - 8.3 Hz, $-C_6\underline{H_4}$-); 7.78 (2 H, d, J = 8.2 Hz, $-C_6\underline{H_4}O$) (Fig. 44, Appendix I).

^{13}C-NMR data ($CDCl_3$): ppm 21.4 (q, $\underline{CH_3}C_6H_4SO_3$-); 68.0, 68.9, 71.9, 72.0, 72.8, 73.3, 73.5, 73.8, 76.9, 77.3, 79.1, 81.2, 83.4 (C-2', C-3', C-4', C-5', C-6', C-1, C-2, C-3, C-4, C-5, C-6 and $-\underline{CH_2}-CH=CH_2$); 102.4 (d, C-1); 115.4, 116.0, 116.4, (t, $-CH_2-CH-\underline{CH_2}$); 127.5, 127.7, 129.5 (d, aryl); 132.5 (s, C-4 aryl); 134.2, 134.5, 135.6 (d, $-CH_2-\underline{CH}=CH_2$); 144.6 (s, C-S Ts) (Fig. 32, Appendix I).

2,3,6-Tri-O-allyl-1,5-anhydro-4-O-(2,3,6-tri-O-allyl-β-D-glucopyranosyl)-D-glucitol (50)

A solution of **68** (3.0 g) in freshly distilled N,N-dimethylformamide (50 mL) containing sodium allylate in allyl alcohol (0.5N, 20 mL) was stirred at 75°C under a nitrogen atmosphere for four hours.[56] The reaction mixture was cooled to room temperature and concentrated in vacuo to dryness. The concentrate was taken up in chloroform (300 mL), washed with water (7 x 400 mL), dried over anhydrous potassium carbonate, and reconcentrated to a sirup. Column chromatography (Merck Kieselgel 60, 70-230 mesh; 2.5 x 80 cm eluent petroleum ether (b.p. 30-60°C)-acetone, 9:1, vol.) gave **50** (1.6 g, 64%) as a sirup.

^{1}H-NMR data ($CDCl_3$): δ 4.90-5.30 (12H, m, $-CH_2-CH=\underline{CH_2}$); 5.50-6.10 (6 H, m, $-CH_2-\underline{CH}=CH_2$) (Fig. 45, Appendix I).

^{13}C-NMR data ($CDCl_3$): ppm 68.0, 70.2, 71.6, 71.9, 72.0, 72.3, 73.6, 76.9, 77.1, 79.2, 81.3, 83.7 (C-2', C-3', C-4', C-5', C-6', C-1, C-2, C-3, C-4, C-5, and C-6); 102.4 (d, C-1'); 115.2, 115.8, 116.2, 116.5 (t, $-CH_2-CH=\underline{CH_2}$); 134.1, 134.6, 134.8, 135.7 (d, $-CH_2-\underline{CH}=CH_2$) (Fig. 33, Appendix I).

Preparation of the Polymer-supported 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3,6-tri-O-allyl-β-D-glucopyranosyl)-D-glucitol (51)

Powdered sodium hydride (0.032 g, 1.33 mmol) was added to a solution of 50 (0.47 g) in freshly distilled tetrahydrofuran (10 mL) under a nitrogen atmosphere. Iodomethylated polystyrene (60) (1.0 g, 3.25 meq CH_2I/g) was added after twenty minutes and the suspension was stirred at room temperature for three days. The disappearance of 50 was monitored by GLC (Conditions A). The beads were isolated by filtration and washed with tetrahydrofuran (2 x 200 mL), transferred to a Soxhlet apparatus and extracted with tetrahydrofuran and hexane, and dried *in vacuo* at 40°C.

The reacted beads (1.0 g) in freshly distilled N,N-dimethylformamide (10 mL) containing sodium ethoxide in ethyl alcohol (0.8N, 50 mL) were stirred at room temperature for 48 hours to convert the unreacted iodomethyl groups to methyl-ethyl ethers. The beads were washed with methanol (4 x 100 mL), acetone (4 x 100 mL), tetrahydrofuran (3 x 100 mL), and hexane (3 x 100 mL) and dried under vacuum at 40°C. The IR spectrum (Fig. 56, Appendix III) indicated absorbances corresponding to C-O stretch at 1091 cm^{-1} (9.17 μm) and olefinic C-H bend at 996 and 923 cm^{-1} (10.0 and 10.8 μm).

Preparation of the Polymer-supported 1,5-anhydro-4-O-β-D-glucopyranosyl-D-glucitol (35)

A slurry of 51 (2.12 g), tristriphenylphosphinerodium chloride (0.45 g), and 1,4-diazabicyclo-[2,2,2]-octane (0.20 g) in a mixture of ethanol-benzene-water (75 mL, 7:3:1, vol.) was refluxed under a nitrogen atmosphere for eight hours.[59] The reaction was cooled to room temperature. The beads were washed with chloroform (3 x 50 mL), tetrahydrofuran (3 x 50 mL), and hexane (2 x 50 mL) and dried under reduced pressure.

The resin was suspended in a mixture of dilute hydrochloric acid (1.2N, 10 mL) and acetone (50 mL), and refluxed for thirty minutes. The slurry was cooled to room temperature and filtered. The beads were washed with acetone (4 x 50 mL), tetrahydrofuran (3 x 100 mL), and hexane (2 x 100 mL), and dried in vacuo at 50°C. The IR spectrum (Fig. 58, Appendix III) showed an O-H absorbance at 3600 to 3200 cm^{-1} and no olefinic absorbances at 996 and 923 cm^{-1} (10.0 and 10.8 μm).

Methyl 2,3-di-O-acetyl-4,6-benzylidene-α-D-glucopyranoside (52)

Methyl α-D-glucopyranoside (47) (10.1 g) was condensed with α,α-dimethoxytoluene (8.6 g) and then acetylated with acetic anhydride and pyridine as described for the synthesis of 64.[54] Crystallization of the crude product from isopropyl alcohol-pyridine (50:1, vol.) gave 52 (14.3 g, 75%): m.p. 100-103°C, $[\alpha]_D$ + 70.5° (c 0.814, $CHCl_3$). Literature: m.p. 108-109°C, $[\alpha]_D$ + 75.5° (c 1.93, $CHCl_3$).[71]

^{1}H-NMR data ($CDCl_3$): δ 2.05 (6 H, 2s, $-COCH_3$); 3.36 (3 H, s, $-OCH_3$); 7.10-7.60 (5.0 H, m, C_6H_5-) (Fig. 46, Appendix I).

^{13}C-NMR data ($CDCl_3$): ppm 20.7 ($-COCH_3$); 55.1 ($-OCH_3$); 62.1, 68.6, 68.8, 71.4, 78.9, (C-2, C-3, C-4, C-5, and C-6); 97.3 (C-1); 101.1, 101.3 [$ArCH(OR)_2$]; 125.8, 127.9, 128.6 (aryl); 136.6 (C-1 aryl); 169.3, 169.9 ($-COCH_3$) (Fig. 34, Appendix I).

Methyl 4,6-O-benzylidene-α-D-glucopyranoside (53)

Compound 52 (4.6 g) was dissolved in chloroform (50 mL) and deacetylated with sodium methoxide in methanol (0.02N, 100 mL) as described for the preparation of 65. Crystallization from isopropyl alcohol-pyridine (50:1, vol.) gave

53 (3.4 g, 96%): m.p. 163-165°C, $[\alpha]_D$ + 110.4° (c 0.90, $CHCl_3$). Literature: m.p. 166-167°C, $[\alpha]_D$ + 110° ($CHCl_3$).[54]

^{1}H-NMR data ($CDCl_3$): δ 3.40 (3 H, s, $-OCH_3$); 4.72 [1 H, d, J = 5.7 Hz, $-CH(OR)(OMe)$]; 5.48 [1 H, s, $ArCH(OR)_2$]; 7.10-7.60 (5 H, m, C_6H_5-) (Fig. 47, Appendix I).

^{13}C-NMR data ($CDCl_3$): ppm 55.5 ($-OCH_3$); 62.4 (C-5); 68.9 (C-6); 71.4 (C-3); 72.7 (C-2); 80.9 (C-4); 99.8 (C-1); 101.8 [$ArCH(OR)_2$]; 126.2, 128.1, 129.0 (aryl); 136.9 (C-1 aryl) (Fig. 35, Appendix I). Literature: ppm 54.9 ($-OCH_3$); 62.0 (C-5); 68.5 (C-6); 70.5 (C-3); 72.4 (C-2); 80.8 (C-4); 99.9 (C-1); 101.5 [$ArCH(OR)_2$].[72]

Methyl 2,3-di-O-allyl-4,6-O-benzylidene-α-D-glucopyranoside (54)

Allylation of 53 in dry N,N-dimethylformamide (50 mL) with sodium hydride and allyl bromide (2 mL) was as described in the preparation of 66.[70] Crystallization from isopropyl alcohol-pyridine (50:1, vol.) gave 54 (2.4 g, 75%): m.p. 63-65°C, $[\alpha]_D$ + 54.7° (c 0.767, $CHCl_3$). Literature: m.p. 62-63°C, $[\alpha]_D$ + 54° (c 0.45, $CHCl_3$).[70]

^{1}H-NMR data ($CDCl_3$): δ 3.42 (3 H, s, $-OCH_3$); 4.76 [1 H, d, J = 3.4 Hz, $-CH(OR)(OMe)$]; 5.00-5.40 (4 H, m, $-CH_2-CH=CH_2$); 5.52 [1 H, s, $ArCH(OR)_2$]; 5.8-6.1 (2 H, m, $-CH_2-CH=CH_2$); 7.1-7.6 (5 H, m, C_6H_5-) (Fig. 48, Appendix I).

^{13}C-NMR data ($CDCl_3$): ppm 55.3 ($-OCH_3$); 62.3 (C-5); 69.0 (C-6); 73.0, 73.8 (C-2, C-3); 77.9, 79.1 ($-CH_2-CH=CH_2$); 82.0 (C-4); 99.2 (C-1); 101.2 [$ArCH(OR)_2$]; 116.5, 117.4 ($-CH_2-CH=CH_2$); 125.9, 128.0, 128.7 (aryl); 134.7, 135.0 ($-CH_2-CH=CH_2$); 137.3 (C-1 aryl) (Fig. 36, Appendix I).

Methyl 2,3-di-O-allyl-6-O-tosyl-α-D-glucopyranoside (55)

Hydrolysis of the benzylidene acetal in 54 followed by selective tosylation of the primary hydroxyl group was as described in the synthesis of 68.[56] Compound 55 was obtained and used as a TLC pure sirup (8.2 g, 75%).

^{1}H-NMR data ($CDCl_3$): δ 2.40 (3 H, s, $CH_3C_6H_4SO_3$-); 3.45 (3 H, s, $-OCH_3$); 5.00-5.40 (4 H, m, $-CH_2-CH=CH_2$); 5.80-6.10 (2 H, m, $-CH_2-CH=CH_2$); 7.31 (2 H, d, J = 8.6 Hz, $-C_6H_4-$); 7.79 (2 H, d, J - 8.2 Hz, $-C_6H_4-$) (Fig. 49, Appendix I).

^{13}C-NMR data ($CDCl_3$): ppm 21.6 ($CH_3C_6H_4SO_3$-); 55.6 ($-OCH_3$); 68.9, 69.3, 72.1, 74.1, 79.1, 80.6 (C-2, C-3, C-4, C-5, C-6, or $-CH_2-CH=CH_2$); 98.0 (C-1); 116.4, 117.5 ($-CH_2-CH=CH_2$); 127.5, 127.9, 129.3, 129.4 (aryl); 132.7 (C-4 aryl); 134.3, 134.7 ($-CH_2-CH=CH_2$); 144.5 (s, C-S, Ts) (Fig. 37, Appendix I).

Methyl 2,3,6-tri-O-allyl-α-D-glucopyranoside (56)

Compound 55 (9.3 g) was dissolved in freshly distilled N,N-dimethylformamide (50 mL) and treated with sodium allylate in allyl alcohol (0.9N, 50 mL) as described for the preparation of 50.[56] Column chromatography (Merck Kieselgel 60, 70-230 mesh; 2.5 x 80 cm; eluent chloroform-ethyl acetate, 10:1, vol.) gave 56 (3.8 g, 57%) as a sirup.

^{1}H-NMR data ($CDCl_3$): δ 3.41 (3 H, s, $-OCH_3$); 4.76 [1 H, d, J - 1.9 Hz, $-CH(OR)(OMe)$]; 5.00-5.40 (6 H, m, $-CH_2-CH=CH_2$); 5.80-6.10 (3 H, m, $-CH_2-CH=CH_2$) (Fig. 50, Appendix I).

^{13}C-NMR data ($CDCl_3$): ppm 54.8 (q, $-OCH_3$); 69.0 (t, C=6); 69.7, 70.1, 79.1, 80.6 (d, C-2, C-3, C-4, C-5); 71.9, 72.2, 73.8 (t, $-CH_2-CH=CH_2$), 97.8 (d, C-1); 116.4, 116.6, 117.1 (t, $-CH_2-CH=CH_2$); 134.2, 134.8 (d, $-CH_2-CH=CH_2$) (Fig. 38, Appendix I).

Methyl 2,3,6-tri-O-allyl-4-O-benzyl-α-D-glucopyranoside (57)

Freshly prepared sodium dimsylate (1.55N, 10 mL) was added to a solution of 56 (3.8 g) in dry dimethyl sulfoxide (50 mL) under a nitrogen atmosphere.[64] The mixture was stirred for sixty minutes at room temperature before the addition of benzyl bromide (4 mL). After twenty four hours the reaction solution was concentrated under reduced pressure (0.45 mm Hg) at 60°C to a solid residue. The residue was dissolved in chloroform (150 mL), washed with water (3 x 250 mL), dried over potassium carbonate, and reconcentrated in vacuo to give 57 as a sirup (5.5 g).

^{1}H-NMR data ($CDCl_3$): δ 3.37 (3 H, s, $-OCH_3$); 5.50-6.15 (3 H, m, $-CH_2-CH=CH_2$); 7.25-7.35 (5 H, m, C_6H_5-) (Fig. 51, Appendix I).

^{13}C-NMR data ($CDCl_3$): ppm 54.8 ($-OCH_3$); 68.3, 69.7, 72.3, 74.0, 77.3, 79.3, 81.4 (C-2, C-3, C-4, C-5, C-6, benzyl C, or $-CH_2-CH=CH_2$); 97.9 (C-1); 115.9, 116.6, 117.0 ($-CH_2-CH=CH_2$); 127.3, 126.8, 127.7 (aryl); 134.1, 134.3, 134.8 ($-CH_2-CH=CH_2$); 137.9 (C-1 aryl) (Fig. 39, Appendix I).

Methyl 4-O-benzyl-α-D-glucopyranoside (49)

Potassium t-butoxide (1.8 g) and 57 (4.1 g) were dissolved in dry dimethyl sulfoxide (50 mL) and stirred under a nitrogen atmosphere at 80°C for three hours.[45] The mixture was cooled to room temperature and diluted with chloroform (200 mL). The chloroform solution was washed with saturated aqueous sodium bicarbonate (4 x 200 mL), dried over anhydrous potassium carbonate, and evaporated under reduced pressure to a sirup. The sirup was dissolved in acetone-water (150 mL, 85:15, vol.) and refluxed with hydrochloric acid (0.2N). After thirty minutes the reaction solution was cooled to room temperature and deionized with ion exchange resin (Baker M-614; H^+, HO^-). The solution was filtered and

the resin was washed with water (2 x 10 mL). The filtrate and water washes were combined and concentrated *in vacuo*. Column chromatography (Merck Kieselgel 60, 70-230 mesh; 2.5 x 50 cm; eluent ethyl acetate) followed by crystallization from ethyl acetate gave **49** (3.5 g, 64%): m.p. 124-126°C, $[\alpha]_D$ + 147.7° (*c* 0.941, CH_3OH). Literature: m.p. 127.5-128.5°C, $[\alpha]_D$ + 146° (*c* 2.2, CH_3OH).[47]

^{13}C-NMR data (CD_3SOCD_3): *ppm* 54.5 (q, $-O\underline{C}H_3$); 60.7 (C-6); 71.4, 72.3, 73.7, 78.3 (C-2-C-5 and benzyl C); 99.6 (C-1); 127.3, 127.9 (aryl); 139.0 (s, C-1 aryl) (Fig. 40, Appendix I).

Methyl 6-O-trityl-α-D-glucopyranoside (**76**)

A solution of methyl α-D-glucopyranoside (**47**) (2.0 g) in anhydrous pyridine (20 mL) was cooled to 0°C and held there while triphenylmethyl chloride (4.0 g) was added with vigorous stirring.[73] The solution was stirred at room temperature for 18 hours and poured into ice water. After thirty minutes the precipitate was isolated by filtration and recrystallized from absolute ethanol to give **76** (2.5 g, 57%): m.p. 151-153°C, $[\alpha]_D$ + 85.0° (*c* 0.95, C_5H_5N). Literature: 151.0-152.0°C, $[\alpha]_D$ + 86.3 (C_5H_5N).[74]

CHARACTERIZATION OF THE SUPPORTED MODEL

Degree of Loading

Ethanolysis

Resin **35** was sealed in screw cap vials (4 mL) with hydrochloric acid (3N, 1.5 mL) and ethanol (1.5 mL) and heated to 100°C for 15 hours. The mixture was then cooled to room temperature and an internal standard, an aqueous solution of D-glucitol (**73**) (5.39 mg/mL), was added gravimetrically. The solution was decanted and the resin was washed with water (2 x 4 mL) and methanol (3 x 4 mL).

The washes were combined and concentrated to dryness under reduced pressure. The residue was diluted with distilled water and reconcentrated (5 x 1 mL). Fresh pyridine (1.5 mL) and acetic anhydride (1.5 mL) were added and the solution was shaken overnight at room temperature. The acetylation mixture was diluted with chloroform (4 mL) and poured into ice water (10 mL). The ice-water and chloroform mixture was stirred for ten minutes and separated. The water layer was extracted with chloroform (2 x 4 mL). The chloroform phases were combined and washed with water (10 mL), dilute hydrochloric acid (0.1N, until the aqueous layer was acidic), saturated aqueous sodium bicarbonate (10 mL), and water (2 x 10 mL), dried over potassium carbonate, and concentrated to a sirup. The sirup was diluted with ethyl acetate (10 drops) and analyzed by GLC (Condition A). The procedure was repeated for 30 and 48 hours. The results are shown in Table 6.

Table 6. Ethanolysis of Resin 35.

Time (hours)	Resin 35 (g)	1,5-Anhydro-D-glucitol (21) (mmol x 10^3)	Loading (meq/g)
15	0.0446	6.907	0.155
30	0.0377	8.577	0.227
48	0.0223	4.932	0.221

Osmylation

A solution of osmium tetraoxide (0.0118 g) in tetrahydrofuran (1.0 mL) was added to a suspension of 51 in pyridine (1 mL).[75] The mixture was allowed to stand at room temperature for four hours. The reaction solution was then removed by aspiration through a syringe needle. The beads were washed with tetrahydrofuran (3 x 5 mL), benzene (3 x 5 mL), and hexane (3 x 5 mL), and dried

under reduced pressure at 40°C. The procedure was repeated on unfunctionalized polystyrene (58). The results are shown in Table 7. The loading was calculated according to Eq. (13).

$$\text{Osmylation loading} = \frac{\dfrac{\text{Weight gain of resin 51}}{\text{g resin 51}} = \dfrac{\text{Weight gain of resin 58}}{\text{g resin 58}}}{\text{(Mw of osmylate ester)*(No. allyl ethers per supported model)}} \quad (13)$$

Table 7. Osmylation of Resins 51 and 58.

Resin	Batch	Wt. Before Osmylation g (A)	Wt. After Osmylation g (B)	Wt. Gain/g (B-A)/A	Loading (meq/g)[a]
51	1	0.0567	0.0948	0.672	2.38
51	1	0.0246	0.0414	0.683	
58	1	0.0608	0.0666	0.096	
58	1	0.0359	0.0388	0.083	
51	2	0.0351	0.0564	0.607	2.44
58	2	0.0460	0.0002	0.004	

[a]Mw of osmylate ester = 412.4 g,[75] average value for loading per batch.

Point of Attachment

The point of polymer-model attachment was determined by the scheme shown in Fig. 27. The experimental procedures used in this scheme are outlined in detail below.

Methylation

Freshly prepared sodium dimsylate (1.25N, 1.0 mL) was added to a slurry of 35 in dry dimethyl sulfoxide (2 mL) under a nitrogen atmosphere.[64] The mixture was allowed to stand at room temperature for thirty minutes before the addition of a solution of methyl iodide (0.1 mL) in dimethyl sulfoxide (1 mL). The

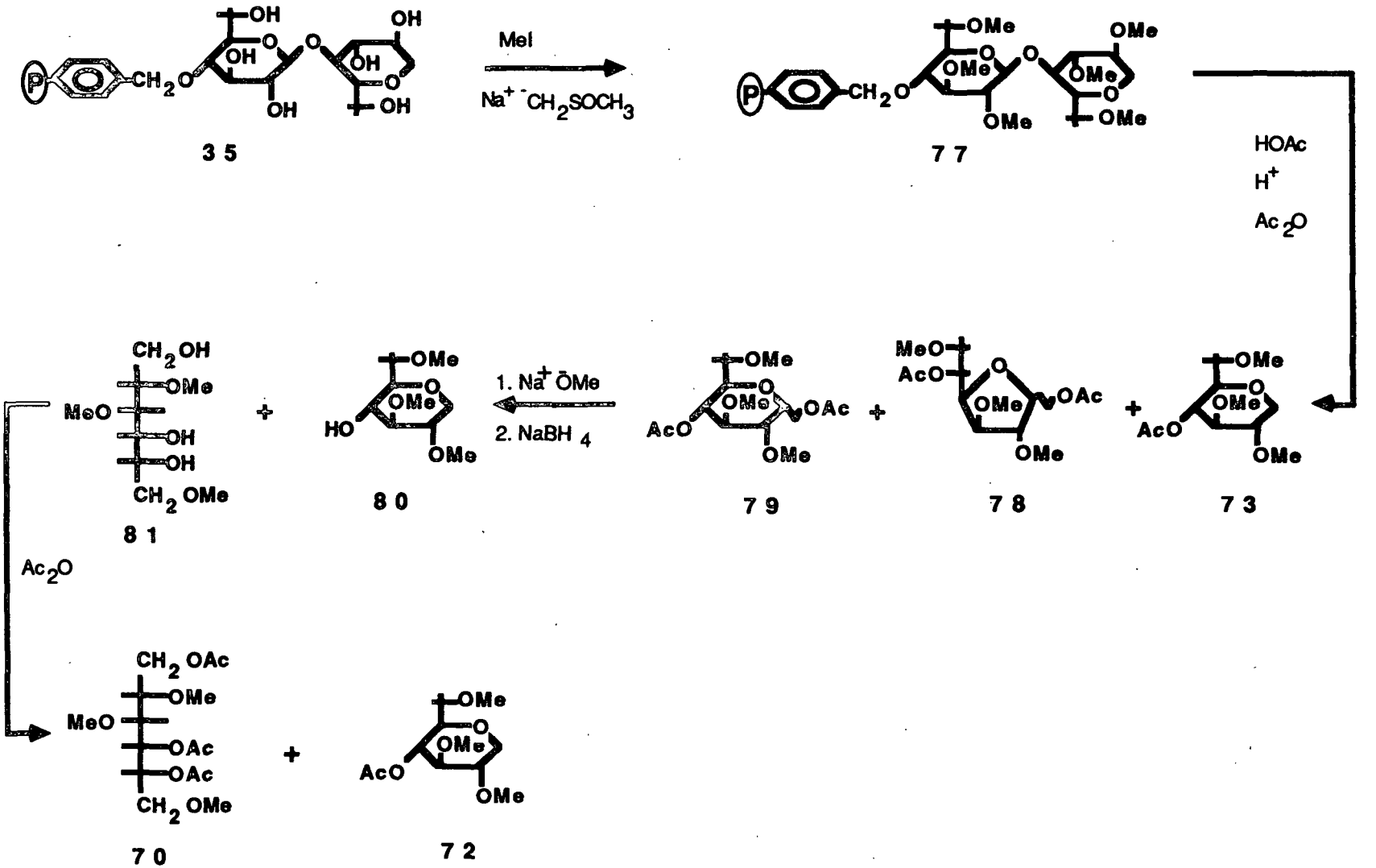


Figure 27. Methylation, acetolysis, deacetylation-reduction, acetylation of the polymer supported model (35).

slurry was sealed and allowed to stand at room temperature for six hours. The dimethyl sulfoxide was removed by aspiration through a syringe needle. The resin was washed with ethanol (3 x 15 mL) and hexane (2 x 10 mL), and dried *in vacuo* at 50°C. This procedure was repeated until infrared analysis showed no OH stretch between 3700 and 3200 cm^{-1} (2.7 and 3.1 μm) (Fig. 59) a total of six times.

Acetolysis

The methylated beads (0.026 g) were treated with glacial acetic acid (0.5 mL), acetic anhydride (0.5 mL), and concentrated sulfuric acid (0.04 mL) at 20°C for 12 hours.[76] The slurry was filtered and the beads were washed with chloroform (2 x 4 mL). The filtrate and chloroform washes were poured into ice water and shaken for five minutes. The products were extracted with chloroform (2 x 5 mL). The chloroform extracts were washed with saturated aqueous sodium bicarbonate (2 x 10 mL) and water (2 x 10 mL) and concentrated under reduced pressure to a residue.

Reduction

The acetolysis residue was dissolved in anhydrous methanol (1 mL) and treated with sodium methoxide (1.0 mL, 0.04*N*). After thirty minutes the solution was cooled to 0°C and sodium borohydride (0.025 g) was added.[77] The mixture was shaken overnight at room temperature, acidified with acetic acid (3 drops), and repeatedly concentrated to dryness under reduced pressure with methanol (5 x 5 mL).

Acetylation

The reduction products were dissolved in acetic anhydride (2 mL) and heated to 100°C for three hours.[78] The acetylation solution was poured into ice water

and extracted with chloroform (2 x 5 mL). The chloroform extracts were washed with saturated sodium bicarbonate (2 x 10 mL), and evaporated to dryness.

Analysis

The acetylation products were dissolved in ethyl acetate and analyzed by GLC and GC/MS (Conditions B and C). Authentic samples of the products expected from the glycosyl portion of the model, 1,4,5-tri-O-acetyl-2,3,6-tri-O-methyl-D-glucitol (70) and 1,5,6-tri-O-acetyl-2,3,4-tri-O-methyl-D-glucitol (69), were prepared in a similar manner from **49** and **76** (Tables 13, 14, and 15).

PRELIMINARY STABILITY CHECKS

Benzyl Ether

The reactor system, developed by Brandon et al.,[16] consisted of a 100 mL capacity, Type 316 stainless steel reactor that could be sampled while hot and under pressure, and an oil-bath assembly that controlled the reactor temperature.

Prior to use all reactor parts were rinsed with acetone, washed with Alconox solution, and rinsed with distilled water. The reactor parts, with the exception of the thermocouple and sample tube, were then heated under vacuum to 100°C for 12 hours to desorb oxygen from the surfaces.

The reactor was loaded with **49** (0.3223 g) and sodium hydroxide (2.76N, 100 mL), assembled, and connected to the sampling system under a nitrogen atmosphere. It was then lowered into the heated oil bath (170.8°C). After the reactor had come to temperature, the sampling system was purged by withdrawing and discarding two samples. The reaction was sampled once a day for twelve days. Prior to each sampling time, the sampling system was purged. Duplicate samples were then collected in tared 4-mL vials. The precise amount of sample taken and

the amount of internal standard, aqueous solution of 2-hydroxyethyl 1-thio-β-D-glucopyranoside (74) (8.5 mmole/g), added were determined gravimetrically.

The samples containing the internal standard were deionized on a column (5 mL) of Amberlite MB-3 (H^+, ^-OH) resin. The samples were eluted from the column with water (10 mL), concentrated in vacuo to dryness, and acetylated with pyridine (1 mL) and acetic anhydride (0.5 mL). The acetylation solutions were shaken mechanically for 12 hours at room temperature. Each sample was diluted with ice water (8 mL), shaken for 30 minutes, and extracted with chloroform (3 x 5 mL). The combined chloroform extracts were washed with water (10 mL) and dilute hydrochloric acid (1.0N, 3 x 8 mL), washed with water (3 x 10 mL), and evaporated under reduced pressure. The samples were diluted with chloroform (0.4 mL) and analyzed by GLC (Conditions D). The experimental data are presented in Table 8.

Table 8. Degradation of methyl 4-O-benzyl-α-D-glucopyranoside (49) in 2.5N sodium hydroxide at 170.8°C.

Time (minutes)	Methyl-4-O-benzyl-α-D-glucopyranoside (49) M	Methyl-α-D-glucopyranoside (47) M
1.3	0.01003	0.00018
469.3	0.00992	0.00022
2501.5	0.00998	0.00019
4396.0	0.00950	0.00018
7217.0	0.00940	0.00022
10149.0	0.00892	0.00030
17581.1	0.00838	0.00018

$\overline{k_r} = 1.050 \times 10^{-5}$ minutes^{-1}.

Polystyrene

The reactor system used consisted of five 4 mL capacity pipe bombs, a controlled temperature oil bath, and a rotating sample rack (Fig. 28). The

bombs were washed with Alconox, rinsed with water and acetone, and dried at 101°C prior to use.

Purified polystyrene beads (58) (≈ 0.050 g) were added gravimetrically to each bomb and the bombs were heated to 101°C under vacuum for four hours, transferred to a nitrogen atmosphere, loaded with sodium hydroxide solution (3.6 g, 2.78N), and sealed. The bombs were then placed in the sample rack and lowered into the oil bath at 170°C. The reaction was sampled at one day intervals for five days.

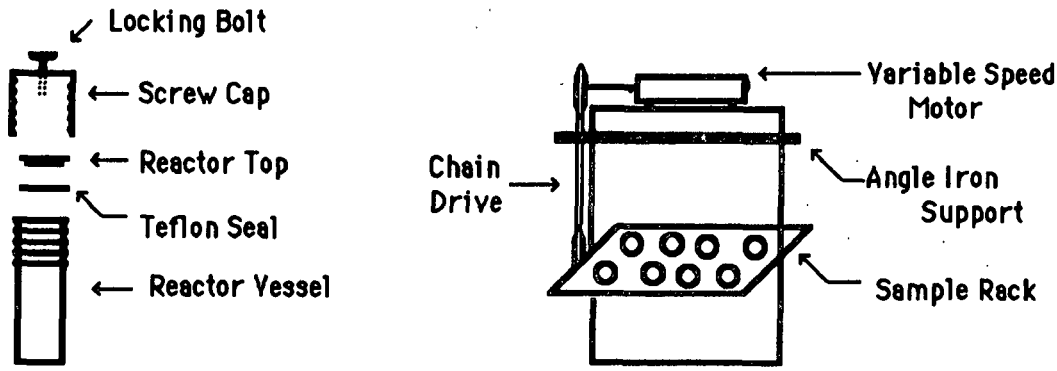


Figure 28. Bomb 4 mL reactors and rotating sample rack.

The beads were isolated by filtration, washed with water until the filtrate remained neutral, and dried *in vacuo*. The recovered yields ranged from 95 to 102%. The beads were then washed with methanol, ether, and benzene; and analyzed on the scanning transmission electron microscope (Fig. 18 and 19).

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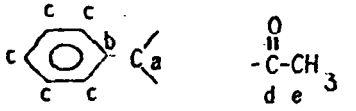
APPENDIX I

NMR SPECTRA

The ^{13}C-NMR and ^{1}H-NMR spectra were obtained for most of the compounds prepared in this study. The assignments were made by comparison to known compounds, and without substantial supporting evidence. Therefore these assignments must be regarded as tentative.

The ^{13}C off resonance splitting patterns are included on several spectra with the notations (s), (d), (t), or (q) indicating singlet, doublet, triplet, or quartet. The ^{13}C chemical shift of the nonanomeric carbohydrate carbons (C-2 → C-6) were not specifically assigned. They appear between 60 and 80 ppm.

Chemical Shift, ppm	Assignment	Chemical Shift, ppm	Assignment
169.8	d	73.5	f
169.6	d	72.3	f
169.4	d	71.6	f
169.0	d	68.8	f
168.8	d	68.2	f
136.1	b	66.8	f
128.8	c	66.4	f
127.8	c	66.0	f
125.7	c	61.8	C-5'
101.1	C-1' and a	20.9	e
78.0	f	20.7	e
77.6	f	20.6	e
76.8	f	20.5	e
75.9	f	19.3	e
75.5	f		



f = C-2', C-3', C-4'C-6', C-1, C-2, C-3, C-4, C-5, or C-6

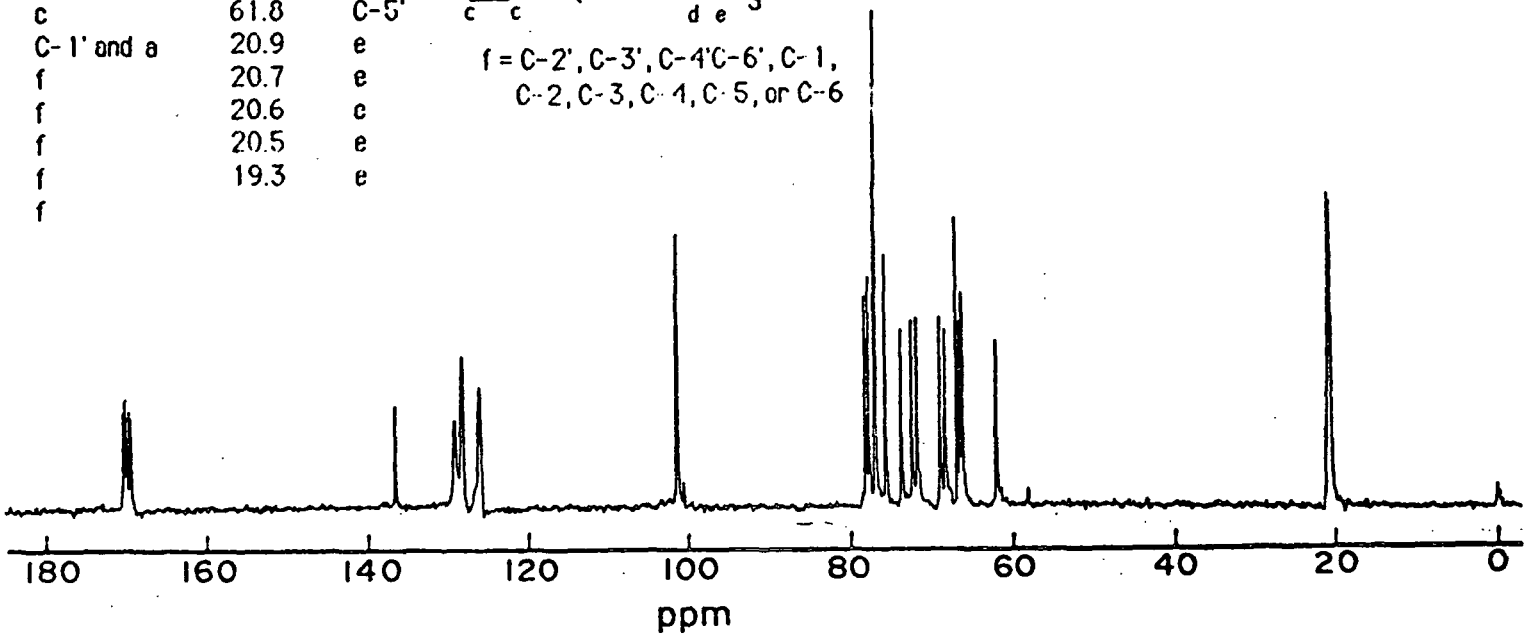
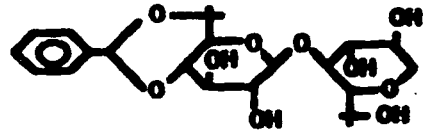
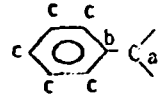


Figure 29. ^{13}C-NMR spectrum of 2,3,6-tri-O-acetyl-1,5-anhydro-4-O-(2,3-di-O-acetyl-4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (64) in d-chloroform.

Chemical Shift, ppm	Assignment
137.4	b
128.6	c
127.7	c
126.1	c
103.0	C-1'
100.6	a
100.5	a
80.2	C-4'
79.4	C-4
76.2	d
74.3	d
72.7	d
69.7	C-1
69.2	C-6'
67.6	d
65.9	d
62.0	$(CH_3)_2\underline{C}HOH$
60.4	C-6
40.4	Dimethyl sulfoxide
39.5	Dimethyl sulfoxide
38.6	Dimethyl sulfoxide
25.5	$(\underline{C}H_3)_2CHOH$





d = C-2', C-3', C-2, C-3, or C-5

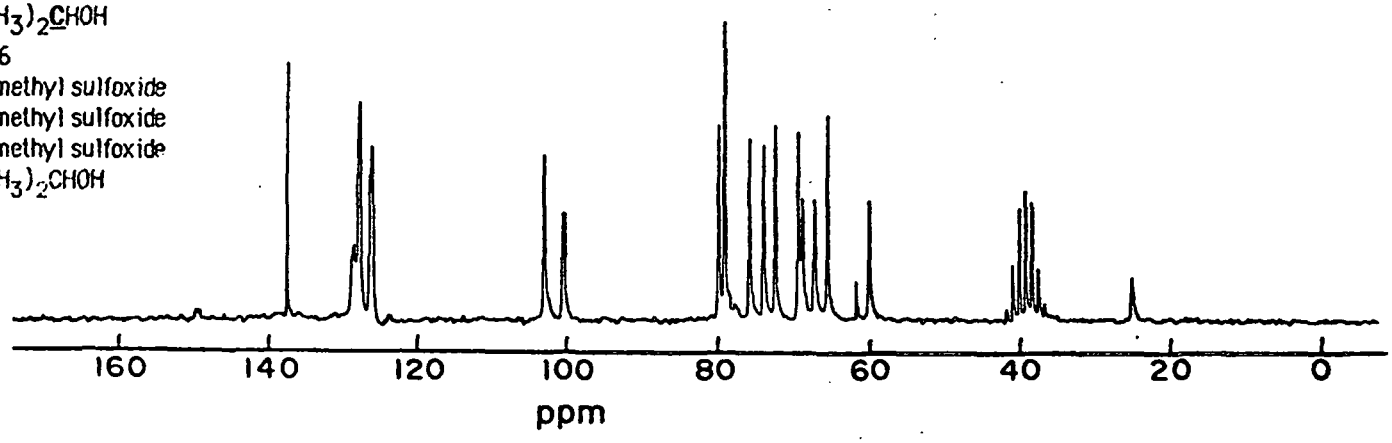


Figure 30. ^{13}C-NMR spectrum of 1,5-anhydro-4-O-(4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (65) in d-dimethyl sulfoxide.

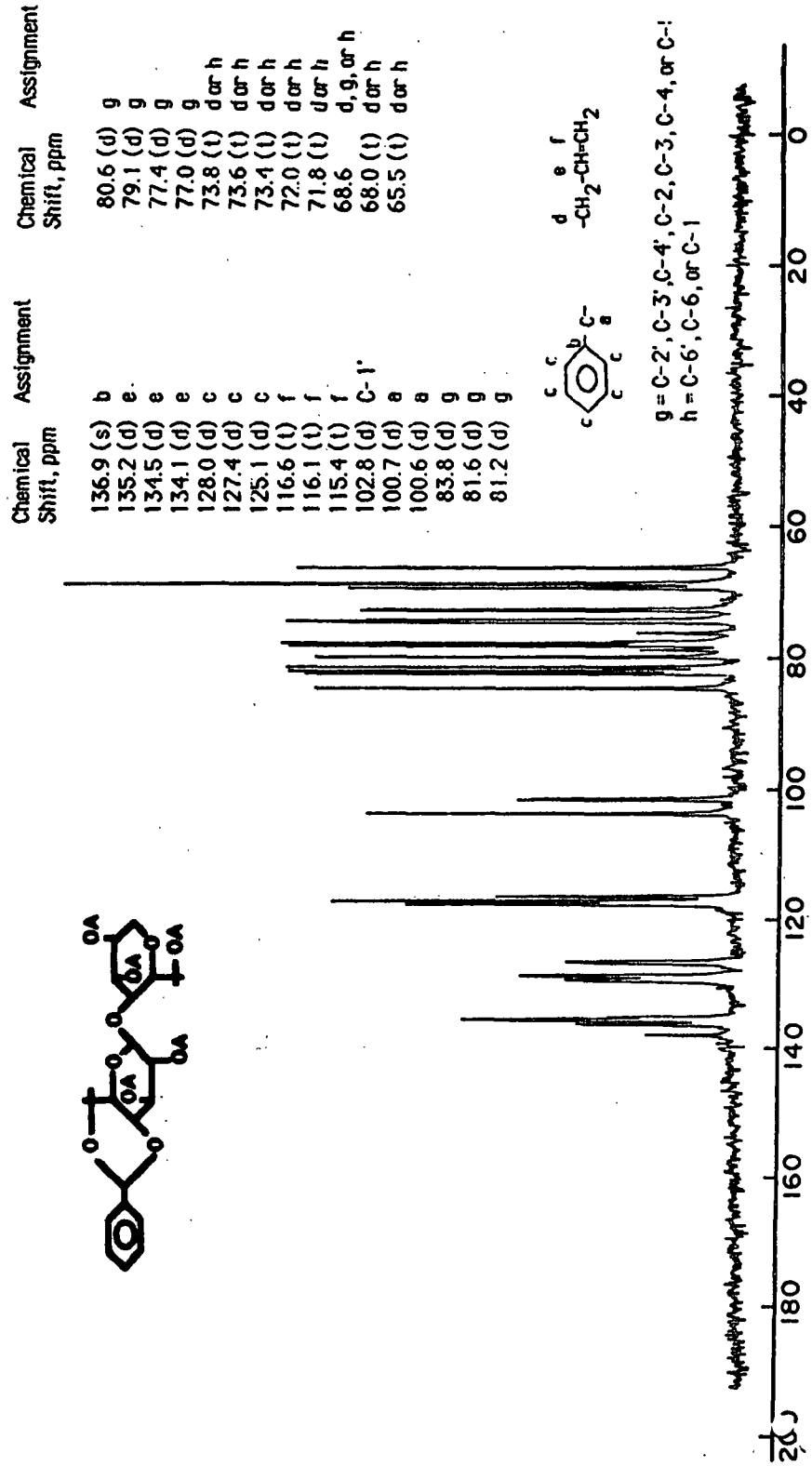
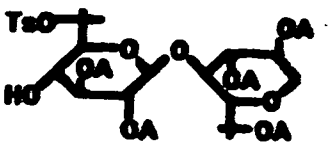
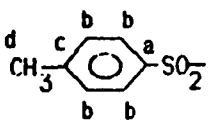
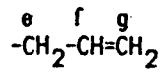


Figure 31. ^{13}C-NMR spectrum of 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3-di-O-allyl-4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (66) in d-chloroform.

Chemical Shift, ppm	Assignment	Chemical Shift, ppm	Assignment
144.6 (s)	a	78.2	Chloroform
135.6 (t)	f	77.3 (d)	h
134.5 (t)	f	76.9 (t)	e or C-1
134.2 (t)	f	75.7	Chloroform
132.5 (s)	c	73.8 (t)	e or i
129.5 (d)	b	73.5 (t)	e or i
127.7 (d)	b	73.3 (t)	e or i
127.5 (d)	b	72.8	e, h, or i
116.4 (t)	g	72.0 (t)	e or i
116.0 (t)	g	71.9 (t)	e or i
115.4 (t)	g	68.9 (d)	h
102.4 (d)	C-1'	68.0 (t)	e or i
83.4 (d)	h	21.4 (q)	d
81.2 (d)	h		
79.1 (d)	h		







h = C-2', C-3', C-4', C-5', C-2, C-3, C-4, or C-5
i = C-6, C-6', or C-1

Figure 32. ^{13}C-NMR spectrum of 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3-di-O-allyl-6-O-tosyl-β-D-glucopyranosyl)-D-glucitol (68) in d-chloroform.

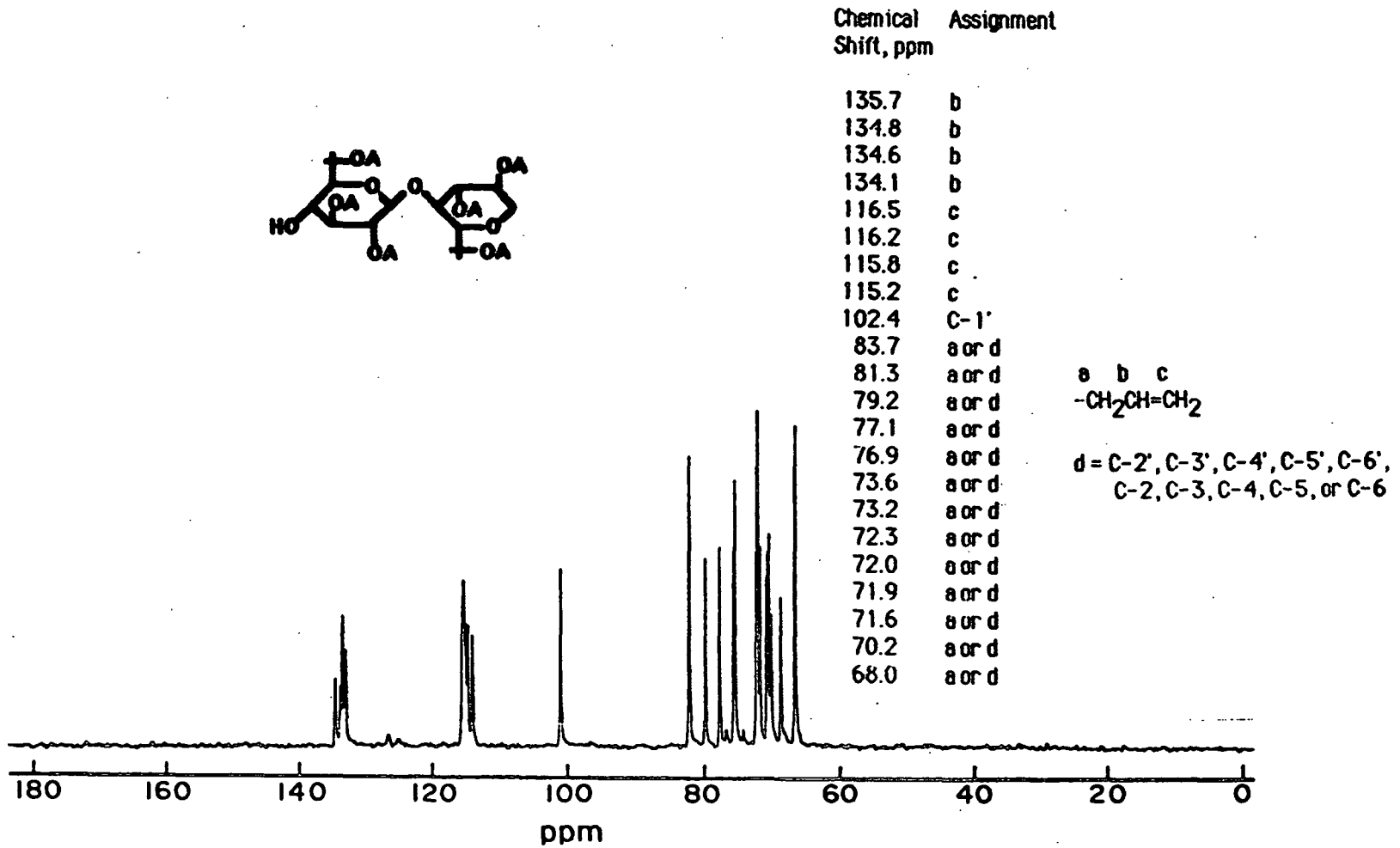


Figure 33. ^{13}C-NMR spectrum of 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3,6-tri-O-allyl-β-D-glucopyranosyl)-D-glucitol (50) in d-chloroform.

Chemical Shift, ppm	Assignment
169.9	d
169.3	d
136.6	b
128.6	c
127.9	c
125.8	c
101.3	a
101.1	a
97.3	C-1
78.9	C-4
78.3	Chloroform
77.0	Chloroform
75.8	Chloroform
71.4	C-2, C-3, or C-6
68.8	C-2, C-3, or C-6
68.6	C-2, C-3, or C-6
62.1	C-5
55.1	$-O\underline{C}H_3$
20.7	e

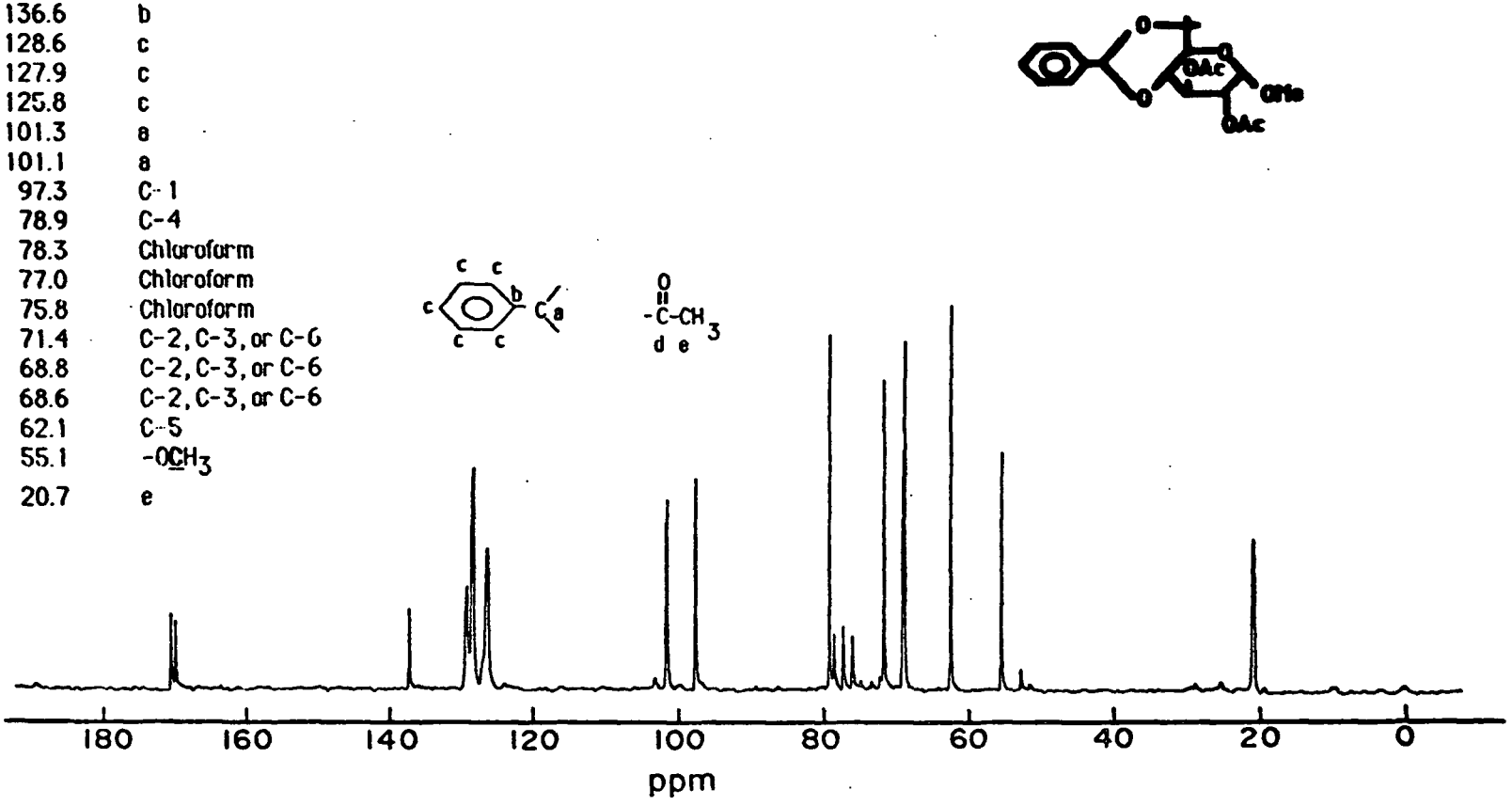


Figure 34. ^{13}C-NMR spectrum of methyl 2,3-di-O-acetyl-4,6-O-benzylidene-α-D-glucopyranoside (52) in d-chloroform.

Chemical Shift, ppm	Assignment
136.9	b
129.0	c
128.1	c
126.2	c
101.8	a
99.8	C-1
80.9	C-4
78.3	Chloroform
77.0	Chloroform
75.7	Chloroform
72.7	C-2
71.4	C-3
68.9	C-6
62.4	C-5
55.5	-O$\underline{C}H_3$

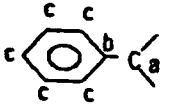
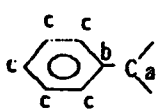


Figure 35. ^{13}C-NMR spectrum of methyl 4,6-$\underline{O}$-benzylidene-α-$\underline{D}$-glucopyranoside (53) in d-chloroform.[72]

Chemical Shift, ppm	Assignment
137.3	b
135.0	e
134.7	e
128.7	c
128.0	c
125.9	c
117.4	f
116.5	f
101.2	a
99.2	C-1
82.0	C-4
79.1	d
78.3	Chloroform
77.9	d
77.0	Chloroform
75.8	Chloroform
73.8	C-2 or C-3
73.0	C-2 or C-3
69.0	C-6
62.3	C-5
55.3	$-OCH_3$



d e f
$-CH_2-CH=CH_2$

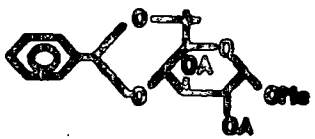


Figure 36. ^{13}C-NMR spectrum of methyl 2,3-di-O-allyl-4,6-O-benzylidene-α-D-glucopyranoside (54) in d-chloroform.

Chemical Shift, ppm	Assignment
144.5	a
134.7	f
134.3	f
132.7	c
129.6	b
127.9	b
127.3	b
127.6	b
117.5	g
116.8	g
103.0	Ar<u>C</u>H(OCH_3)$_2$, impurity
98.0	C-1
80.9	e or h
79.1	Chloroform
77.0	Chloroform
75.7	Chloroform
74.1	e or h
72.1	e or h
69.3	e or h
68.9	e or h
55.6	-O<u>C</u>H_3
52.6	ArCH(O<u>C</u>H_3)$_2$, impurity
21.6	d

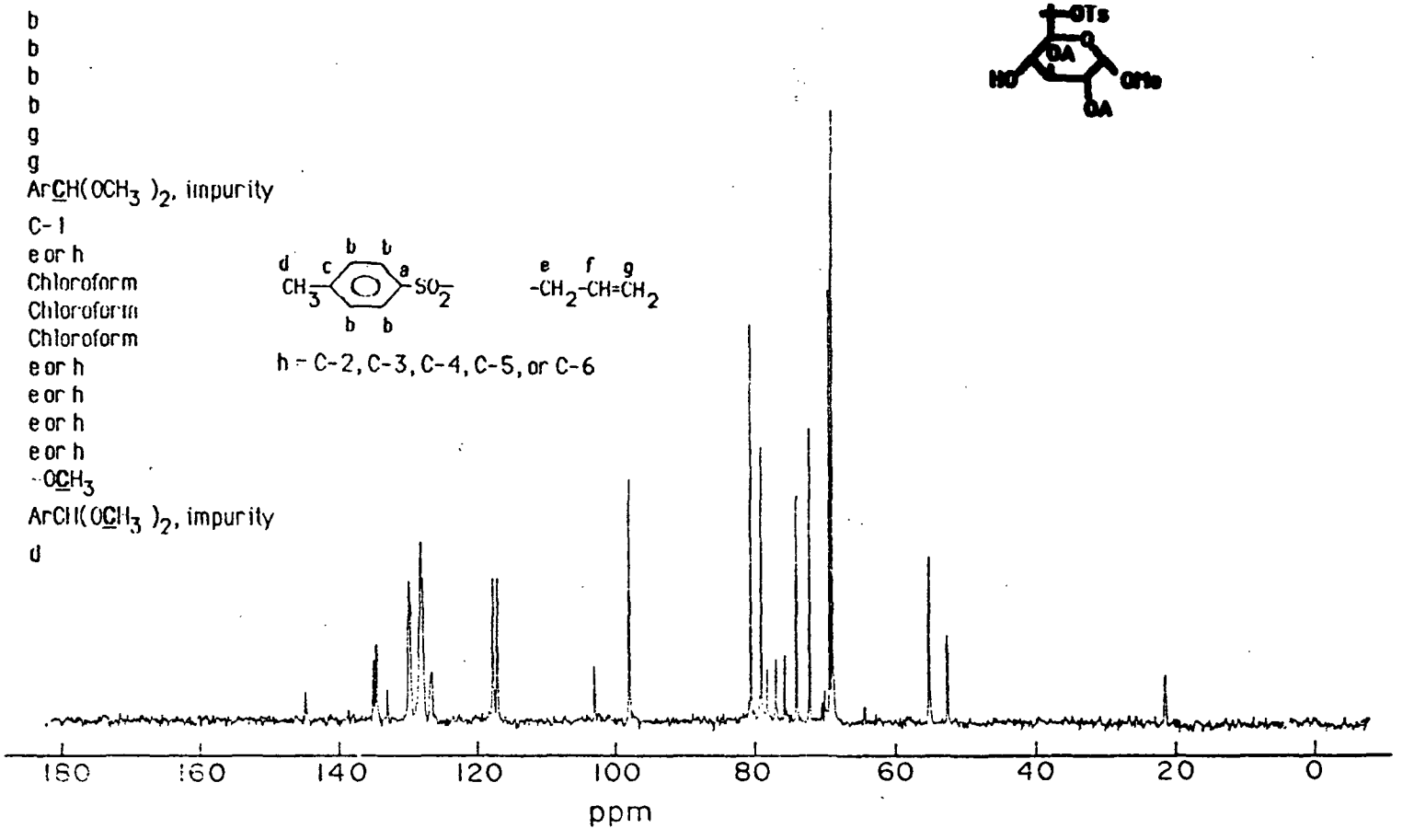


Figure 37. ^{13}C-NMR spectrum of methyl 2,3-di-<u>O</u>-allyl-6-<u>O</u>-tosyl-α-<u>D</u>-glucopyranoside (55) in d-chloroform.

Chemical Shift, ppm	Assignment
134.8 (d)	b
134.2 (d)	b
117.1 (t)	c
116.6 (t)	c
116.4 (t)	c
97.8 (d)	C-1
80.6 (d)	C-2, C-3, C-4, or C-5
79.1 (d)	C-2, C-3, C-4, or C-5
77.0	Chloroform
73.8 (t)	a
72.2 (t)	a
71.9 (t)	a
70.1 (d)	C-2, C-3, C-4, or C-5
69.7 (d)	C-2, C-3, C-4, or C-5
69.0 (t)	C-6
54.8 (q)	$-OCH_3$

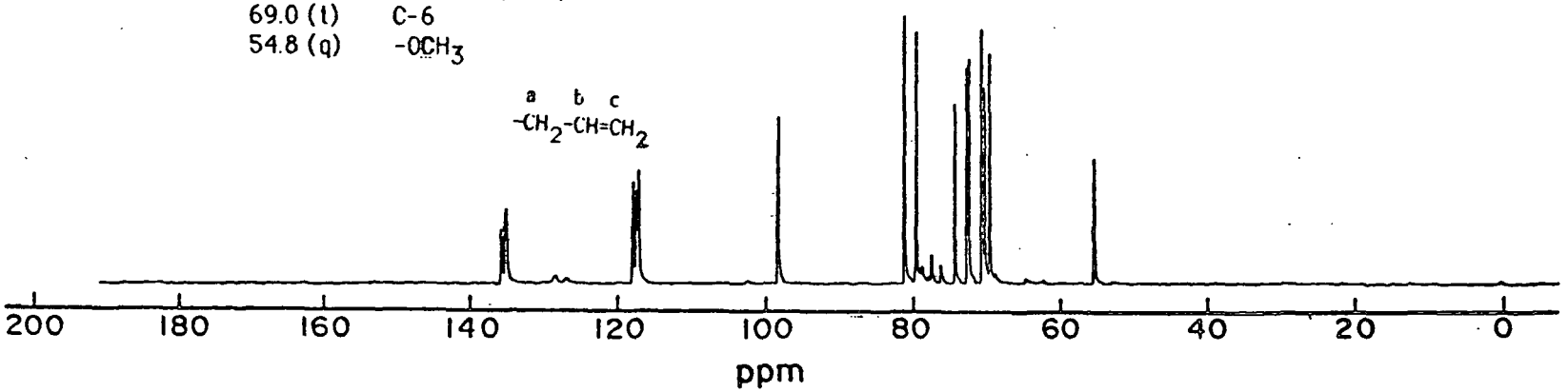
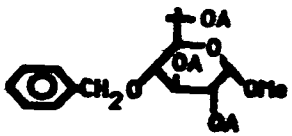
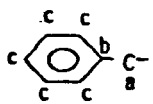


Figure 38. ^{13}C-NMR spectrum of methyl 2,3,6-tri-O-allyl-α-D-glucopyranoside (56) in d-chloroform.

Chemical Shift, ppm	Assignment
137.9	b
134.8	e
134.1	e
126.8	c
127.3	c
117.0	f
116.6	f
115.9	f
97.7	C-1
81.2	a, d, or g
79.2	a, d, or g
77.2	a, d, or g
77.0	Chloroform
74.6	a, d, or g
73.8	a, d, or g
72.1	a, d, or g
69.6	a, d, or g
68.2	a, d, or g
54.6	$-O\underline{C}H_3$



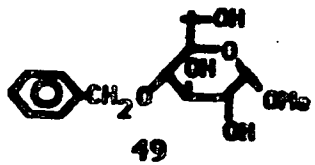


d e f
$-CH_2-CH=CH_2$

g = C-2, C-3, C-4, C-5 or C-6

Figure 39. ^{13}C-NMR spectrum of methyl 2,3,6-tri-O-allyl-4-O-benzyl-α-D-glucopyranoside (57) in d-chloroform.

Chemical Shift, ppm	Assignment
139.0	b
127.9	c
127.3	c
99.6	C-1
78.3	C-2, C-3, C-4, C-5, or a
73.7	C-2, C-3, C-4, C-5, or a
72.3	C-2, C-3, C-4, C-5, or a
71.4	C-2, C-3, C-4, C-5, or a
60.7	C-6
54.5	$-O\underline{C}H_3$
40.4	Dimethyl sulfoxide
39.5	Dimethyl sulfoxide
38.7	Dimethyl sulfoxide



49

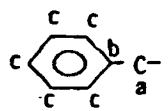


Figure 40. ^{13}C-NMR spectrum of methyl 4-O-benzyl-α-D-glucopyranoside (49) in d-dimethyl sulfoxide.

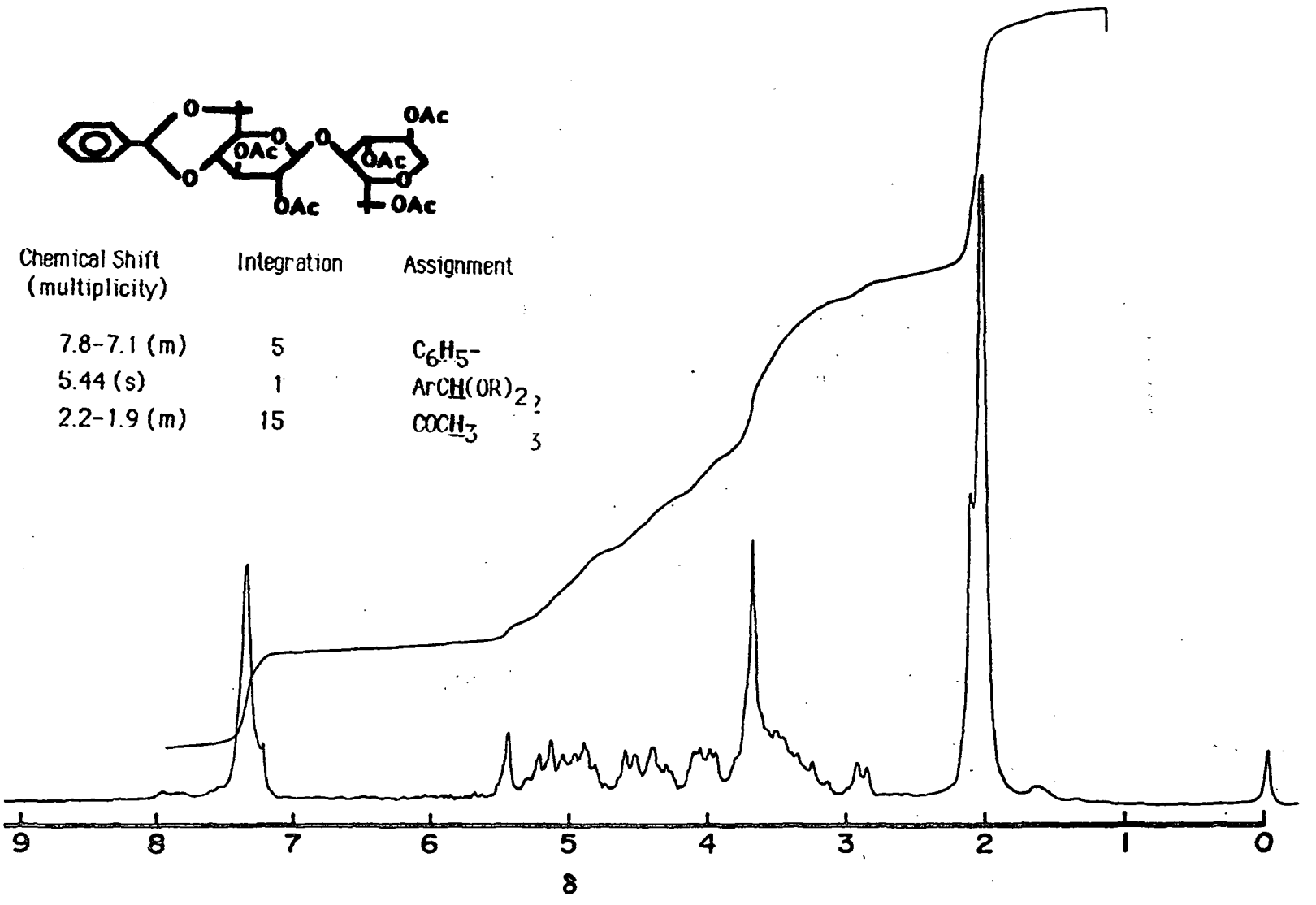


Figure 41. ^{1}H-NMR spectrum of 2,3,6-tri-O-acetyl-1,5-anhydro-4-O-(2,3-di-O-acetyl-4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (64) in d-chloroform.

Chemical Shift (multiplicity)	Integration	Assignment
7.6-7.1 (m)	5.0	$C_6\underline{H}_5$-
5.66 (s)	1.0	$C_6H_5C\underline{H}(OR)_2$
1.3-1.0	1.0	$HOCH(C\underline{H}_3)_2$

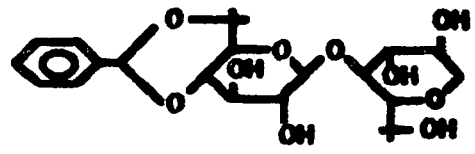
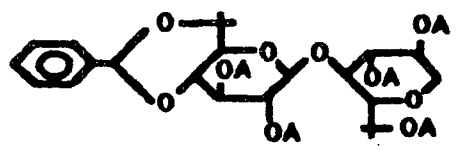
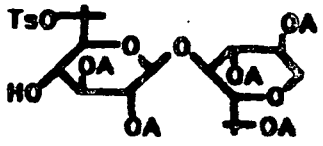


Figure 42. ^{1}H-NMR spectrum of 1,5-anhydro-4-O-(4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (65) in d-dimethyl sulfoxide.



Chemical Shift (multiplicity)	Integration	Assignment
7.7-7.3 (m)	6	$C_6\underline{H}_5$- + $C\underline{H}Cl_3$
6.1-5.8 (m)	5	-CH_2-$C\underline{H}$=CH_2
5.52 (s)	1	$C_6H_5C\underline{H}(OR)_2$
5.5-5.0 (m)	10	-CH_2-CH=$C\underline{H}_2$

Figure 43. ^{1}H-NMR spectrum of 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3-di-O-allyl-4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (66) in d-chloroform.



Chemical Shift (multiplicity, J)	Integration	Assignment
7.78 (d, 8.2 Hz)	2	$CH_3C_6\underline{H}_4SO_3$-
7.32 (d, 8.3 Hz)	2	$CH_3C_6\underline{H}_4SO_3$-
6.1-5.5 (m)	5	-CH_2-C$\underline{H}$=CH_2
5.3-5.0 (m)	10	-CH_2-CH=C$\underline{H}_2$
2.43 (s)	3	C$\underline{H}_3C_6H_4SO_3$-

Figure 44. ^{1}H-NMR spectrum of 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3-di-O-allyl-6-O-tosyl-β-D-glucopyranosyl)-D-glucitol (68) in d-chloroform.

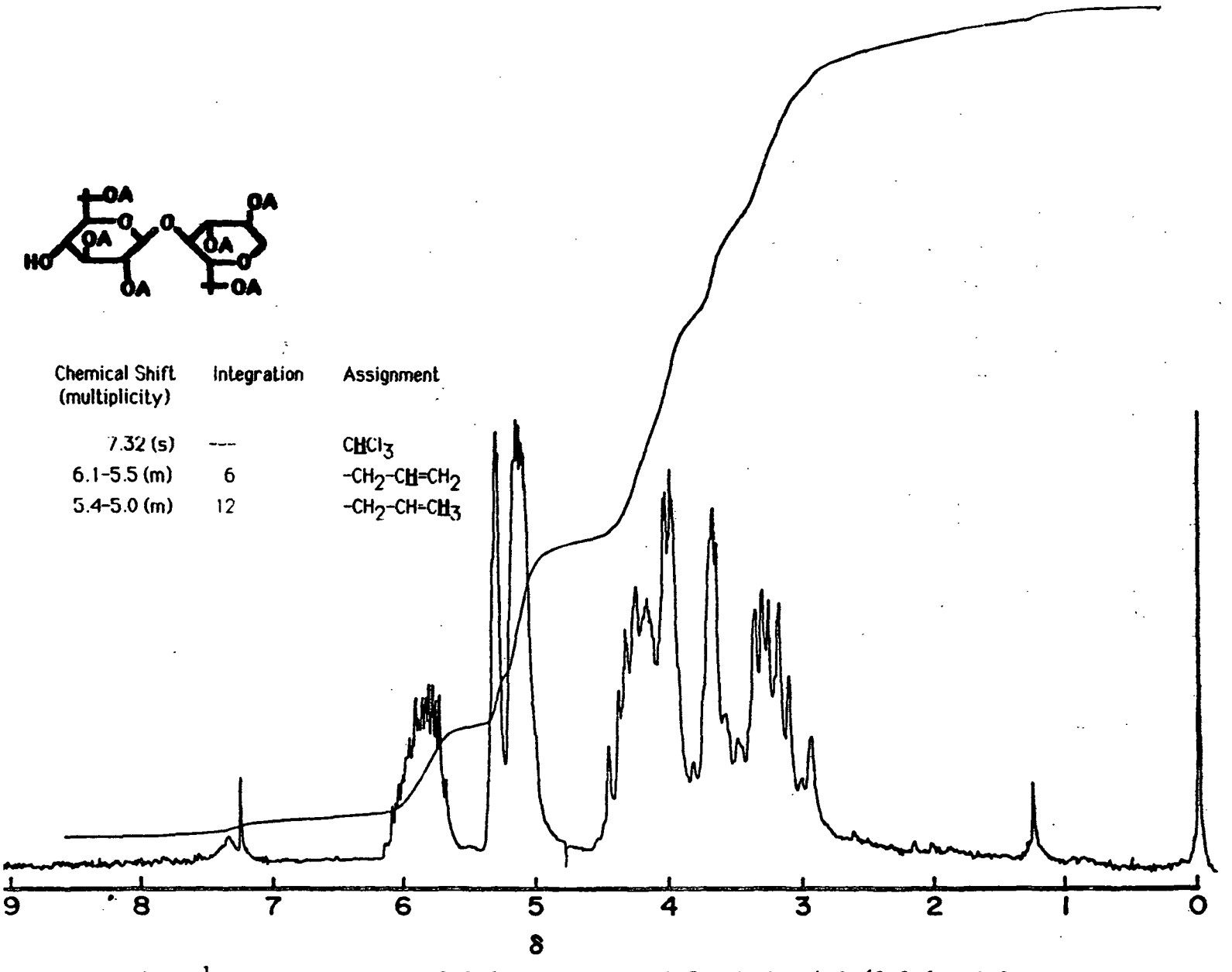


Figure 45. ^{1}H-NMR spectrum of 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3,6-tri-O-allyl-β-D-glucopyranosyl)-D-glucitol (50) in d-chloroform.

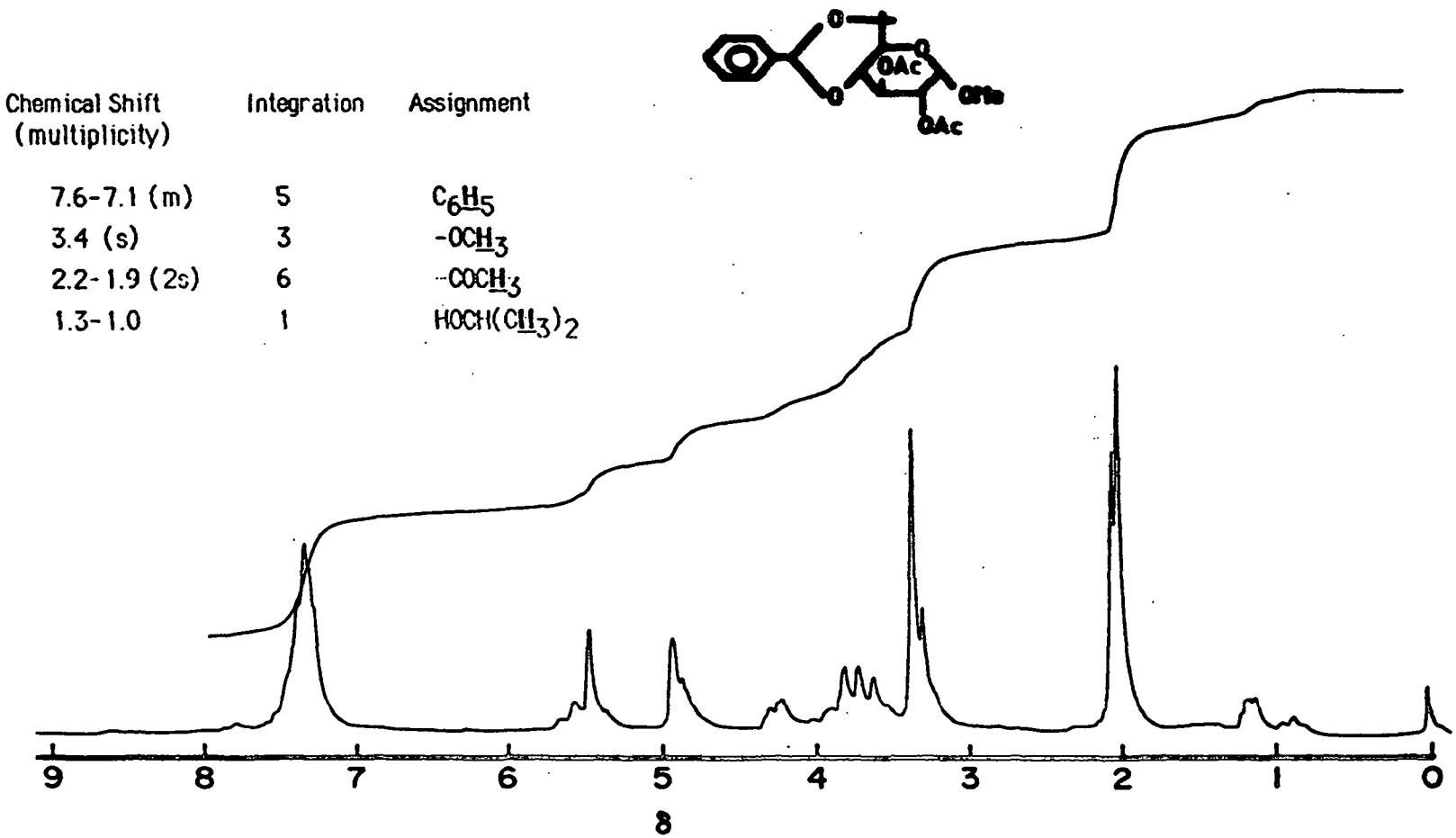
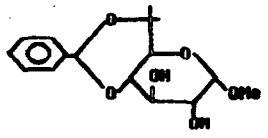


Figure 46. ^{1}H-NMR spectrum of methyl 2,3-di-O-acetyl-4,6-benzylidene-α-D-glucopyranoside (52) in d-chloroform.



Chemical Shift (multiplicity, J)	Integration	Assignment
7.6-7.1 (m)	5	$C_6\underline{H}_5$-
5.48 (s)	1	$ArC\underline{H}(OR)_2$
4.72 (d, 5.7 Hz)	1	$C\underline{H}(OR)(OCH_3)$
3.40 (s)	3	$-OC\underline{H}_3$

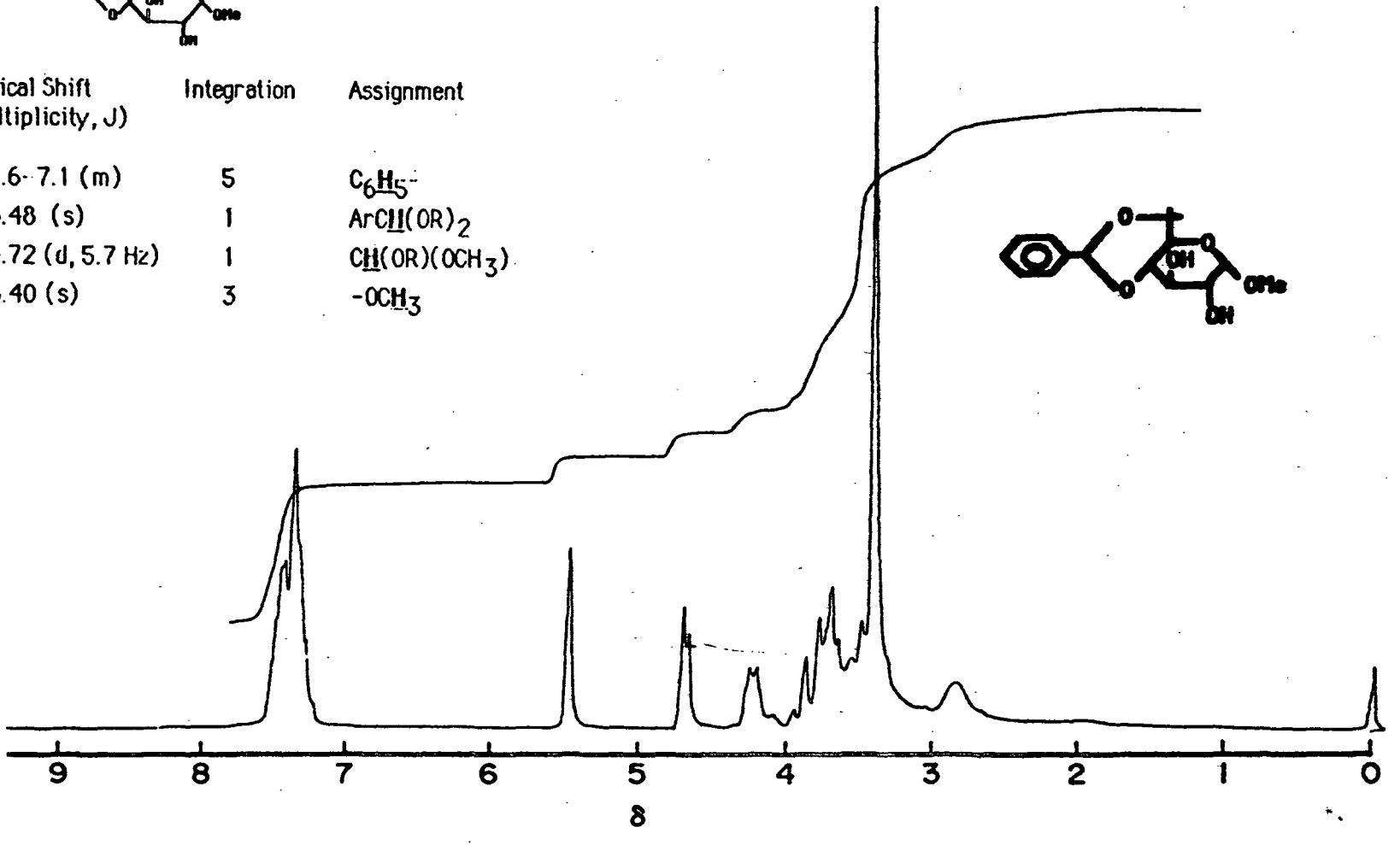
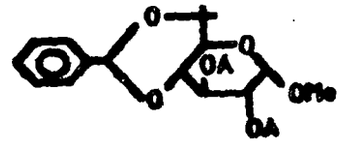


Figure 47. ^{1}H-NMR spectrum of methyl 4,6-benzylidene-α-D-glucopyranoside (53) in d-chloroform.



Chemical Shift (multiplicity, J)	Integration	Assignment
7.6-7.1 (m)	5	$C_6\underline{H}_5$-
6.1-5.8 (m)	2	$-CH_2-C\underline{H}=CH_2$
5.52 (s)	1	$C_6H_5C\underline{H}(OR)_2$
5.4-5.0 (m)	4	$-CH_2-CH=C\underline{H}_2$
4.76 (d, 3.4 Hz)	1	$C\underline{H}(OR)(OCH_3)$
3.42 (s)	3	$-OC\underline{H}_3$

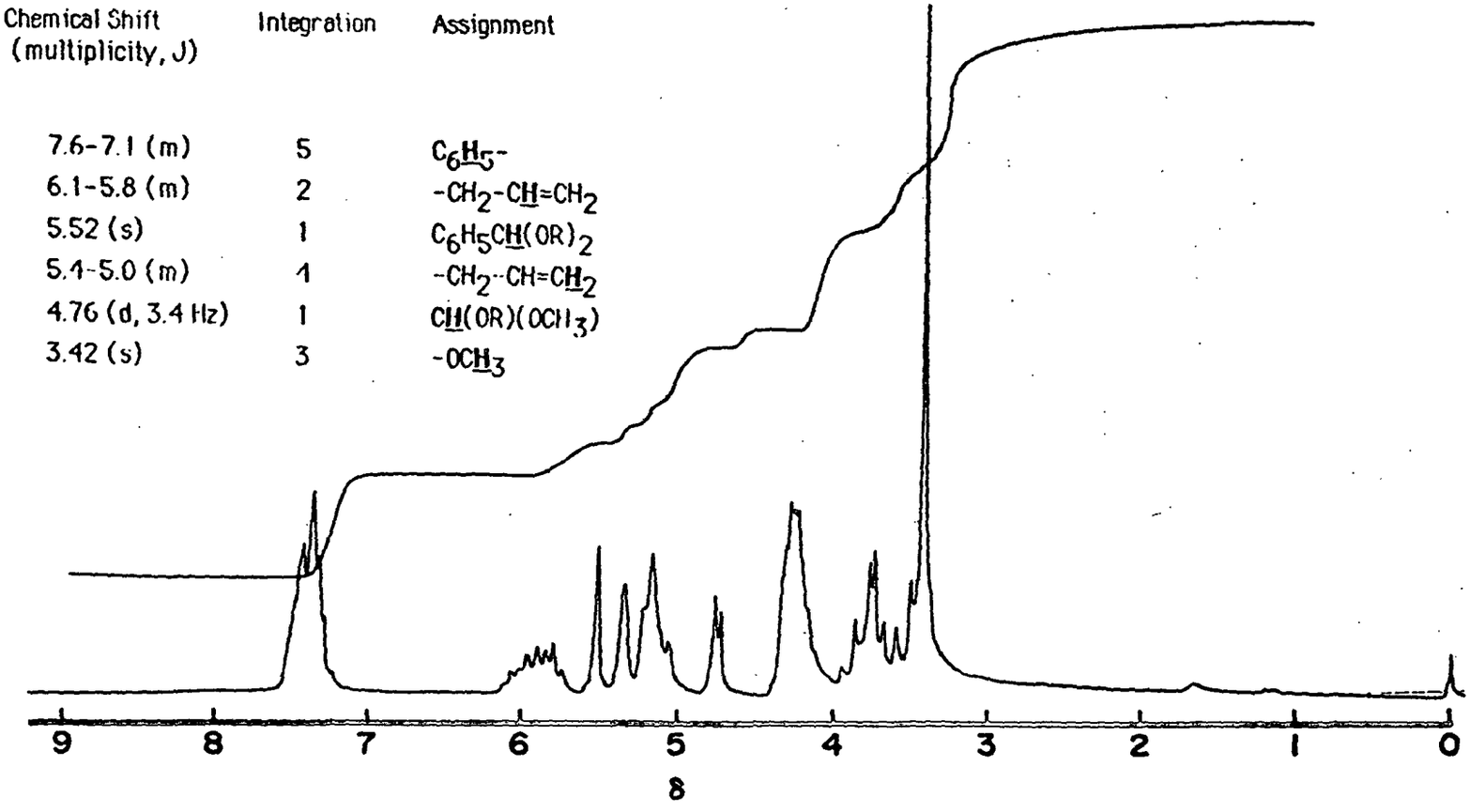
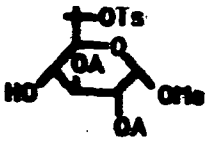


Figure 48. ^{1}H-NMR spectrum of methyl 2,3-di-O-allyl-4,6-benzylidene-α-D-glucopyranoside (54) in d-chloroform.



55

Chemical Shift (multiplicity)	Integration	Assignment
7.79 (d, 8,2 Hz)	2	$CH_3C_6\underline{H}_4SO_3$-
7.31 (d, 8.3 Hz)	2	$CH_3C_6\underline{H}_4SO_3$-
6.1-5.8 (m)	2	$-CH_2-C\underline{H}=CH_2$
5.4-4.9 (m)	4	$-CH_2-CH=C\underline{H}_2$
3.45 (s)	3	$-OC\underline{H}_3$
2.40 (s)	3	$C\underline{H}_3C_6H_4SO_3$-

Figure 49. ^{1}H-NMR spectrum of methyl 2,3-di-O-allyl-6-O-tosyl-α-D-glucopyranoside (55) in d-chloroform.

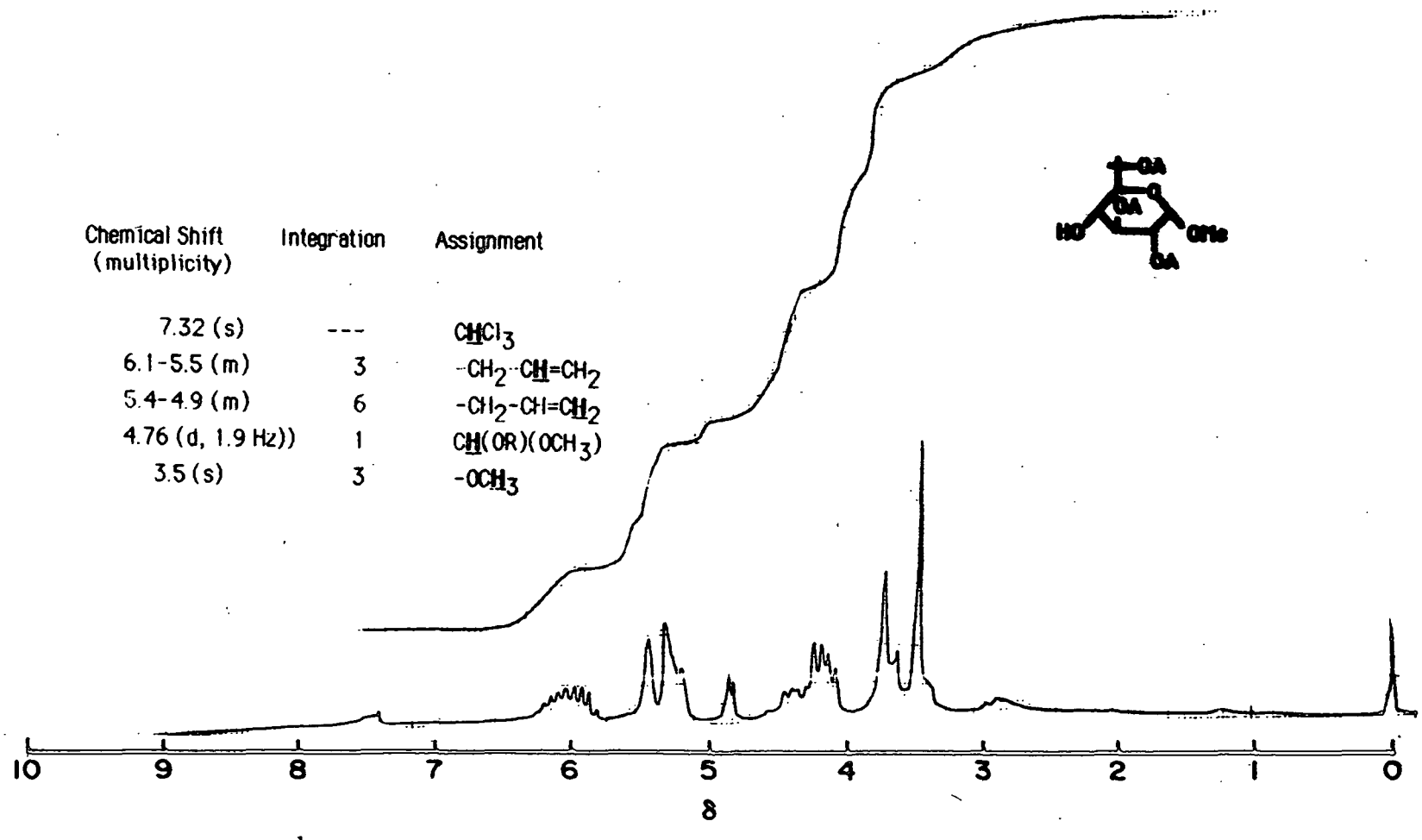


Figure 50. ^{1}H-NMR spectrum of methyl 2,3,6-tri-O-allyl-α-D-glucopyranoside (56) in d-chloroform.

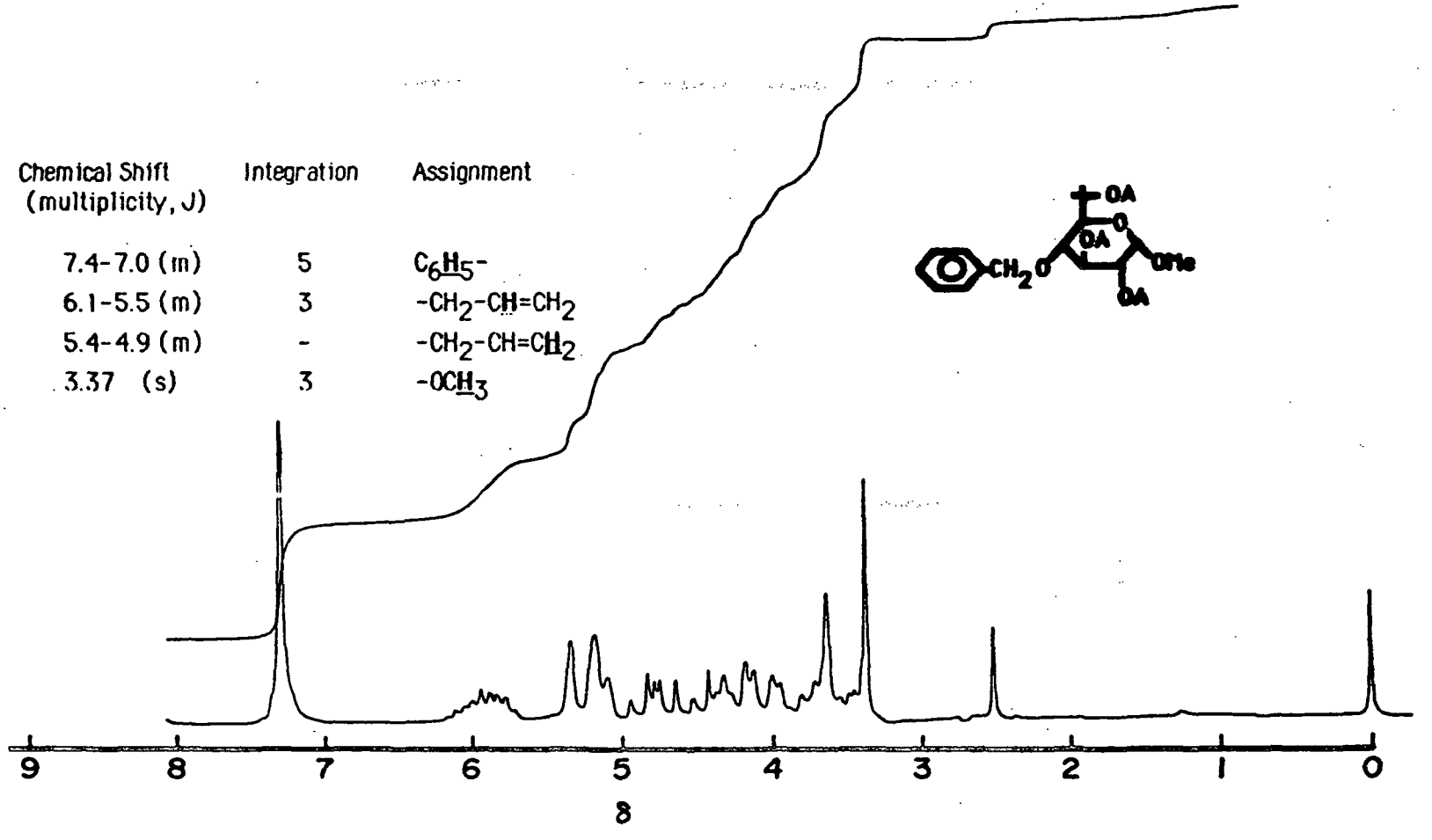


Figure 51. ^{1}H-NMR spectrum of methyl 2,3,6-tri-O-allyl-4-O-benzyl-α-D-glucopyranoside (57) in d-chloroform.

APPENDIX II

MASS SPECTRA

The El mass spectra of 2,3,6-tri-O-acetyl-1,5-anhydro-4-O-(2,3-di-O-acetyl-4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (64), 1,5-anhydro-4-O-(4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (65), and 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3-di-O-allyl-4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (66) were obtained. With the exception of 64, they did not show molecular ions. Primary fragments were formed by fission on both sides of the glucosidic bond and by fission of the benzylidene acetal (Fig. 52).[55,81] The secondary fragments were formed by elimination of the acetate groups as acetic acid (M-60), ketene (M-42), or acetyl radical (M-59); allyl ethers as allyl alcohol (M-58); and hydroxyl groups as water (M-18).

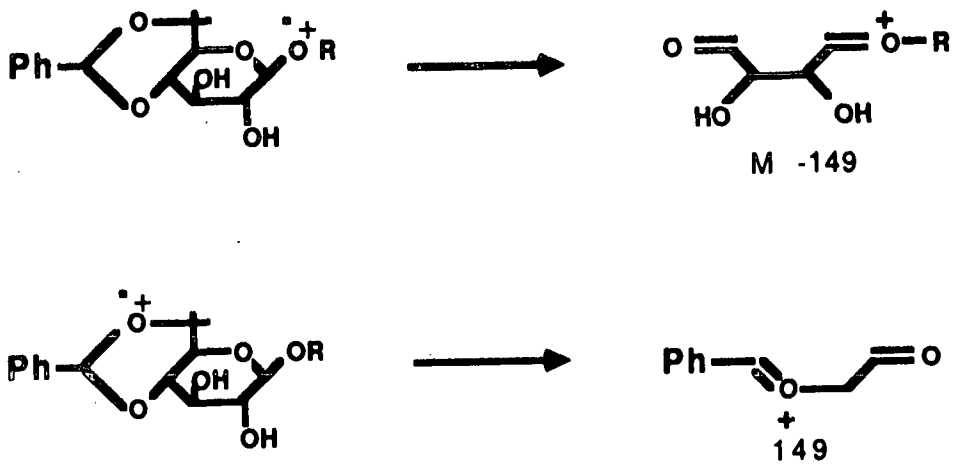


Figure 52. Mass spectrum (El) fragmentation pattern of 4,6-benzylidenes.[55,81]

The El mass spectra of the partially methylated alditol acetates 71, 72, and 73 were also obtained. Primary fragments in the first two were formed by fission between the carbon atoms in the alditol chain. In general, this process occurs most readily between two methoxylated carbon atoms. When fission occurs

between an acetoxylated and a methoxylated carbon atom the charge remains on the methoxylated carbon.[55] Secondary fragments in all three compounds were formed by elimination of methanol (M-32), acetic acid (M-60), and ketene (M-42).

Table 9. Mass spectrum (E1) of 2,3,6-tri-O-acetyl-1,5-anhydro-4-O-(2,3-di-O-acetyl-4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (64).

M/E	Relative Abundance	Assignment
624	0.6	M
475	1.2	M-149
335	3.5	Glycone
275	7.6	335 - AcOH
273	41.3	Aglycone
171	5.5	273 - AcOH-CH_2CO
149	23.0	$C_6H_5CH{=}O{-}CH{=}O$
105	25.6	$C_6H_5C{=}O$
91	7.5	$C_6H_5CH_2$
43	100.0	Ac

Table 10. Mass spectrum (E1) of 1,5-anhydro-4-O-(4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (65).

M/E	Relative Abundance	Assignment
265	4.9	M-149
235	6.6	265 - CH_2=O
251	3.0	Glycone
193	35.6	
175	19.4	193 - H_2O
165	14.6	
162	17.1	
149	12.4	C_6H_5CH=O-CH=O
147	15.1	Aglycone
133	10.0	
129	12.3	147 - H_2O
121	10.7	
107	100.0	
106	17.1	C_6H_5CH=O
105	85.3	C_6H_5C=O
91	24.8	$C_6H_5CH_2$
79	22.3	C_6H_7
77	17.3	C_6H_5
73	64.3	
71	13.3	
69	49.3	
45	21.0	
43	28.6	

Table 11. Mass spectrum (El) of 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3-di-O-allyl-4,6-O-benzylidene-β-D-glucopyranosyl)-D-glucitol (66).

M/E	Relative Abundance	Assignment
353	14.5	
331	1.1	Glycone
267	2.1	Aglycone
209	3.4	267 - AlOH
169	3.1	
167	3.2	
153	10.9	
151	4.6	209 - AlOH
149	7.5	$C_6H_5CH{=}O{-}CH{=}O$
147	5.9	
141	5.5	
140	39.5	
139	6.6	
127	6.7	
125	7.6	
124	6.5	
113	9.5	
111	19.9	
107	9.5	
105	22.8	$C_6H_5C{=}O$
101	9.6	
99	10.6	
97	24.4	
96	8.2	
91	16.5	$C_6H_5CH_2$
85	16.5	
84	7.7	
83	21.4	
81	45.3	
79	22.3	C_6H_7
77	17.3	C_6H_5
41	100.0	$C_3H_5^+$

Table 12. Mass spectrum (E1) 4-O-acetyl-1,5-anhydro-2,3,6-tri-O-methyl-D-glucitol (72).

M/E	Relative Abundance	Assignment
248	0.5	M
203	42.6	M - $\cdot CH_2OMe$
189	3.7	M - AcO$\cdot$
171	73.4	203 - MeOH
143	80.3	203 - AcOH
129	83.2	171 - CH_2CO
125	2.2	189 - MeOH-MeOH
117	10.1	
111	24.7	143 - MeOH
101	30.0	
97	100.0	129 - MeOH
88	26.1	
87	67.9	
85	43.5	
75	47.0	
74	38.0	
73	17.4	
58	68.9	
45	51.2	CH_2OMe
43	84.3	Ac

Table 13. Mass spectrum (E1) of 1,4,5-tri-O-acetyl-2,3,6-tri-O-methyl-D-glucitol (70) from methylation-hydrolysis of methyl 4-O-benzyl-α-D-glucopyranoside (49).

M/E	Relative Abundance	Assignment
233	54.7	*
189	0.4	*
173	8.8	233 - AcOH
161	9.9	*
159	3.1	
145	0.3	
143	5.9	
142	7.8	
131	14.5	173 - CH_2CO
130	1.8	
129	16.6	161 - MeOH
127	2.4	
117	100.0	*
114	3.8	
113	39.2	
111	3.1	
101	30.9	161 - AcOH
100	3.2	
99	26.5	131 - MeOH
88	5.5	
87	22.9	129 - CH_2CO
85	8.0	
71	7.9	101 - CH_2CO
45	12.1	*
43	63.4	Ac

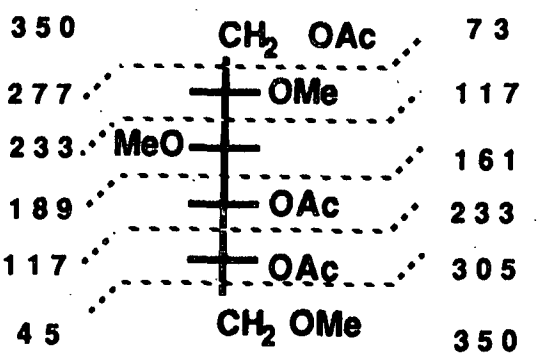


Table 14. Mass spectrum (El) of 1,5,6-tri-O-acetyl-2,3,4-tri-O-methyl-D-glucitol (70) from methylation-hydrolysis of methyl 6-O-trityl-α-D-glucopyranoside (76).

M/E	Relative Abundance	Assignment
233	7.4	*
189	21.1	*
173	6.6	233 - AcOH
161	32.4	*
159	4.6	
145	1.0	*
143	2.3	
142	1.5	
131	6.8	173 - CH_2CO
130	9.8	
129	48.5	161 - MeOH
127	0.9	
117	83.8	*
114	1.3	
113	8.5	
111	2.0	
101	100.0	161 - AcOH
100	5.6	
99	52.6	131 - MeOH
88	14.6	
87	47.0	129 - CH_2CO
85	3.8	
71	11.9	101 - CH_2CO
45	9.4	CH_2OMe
43	97.1	Ac

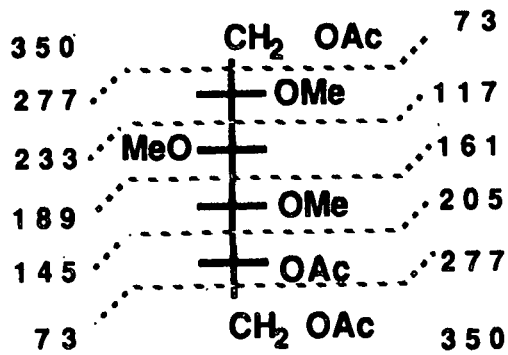
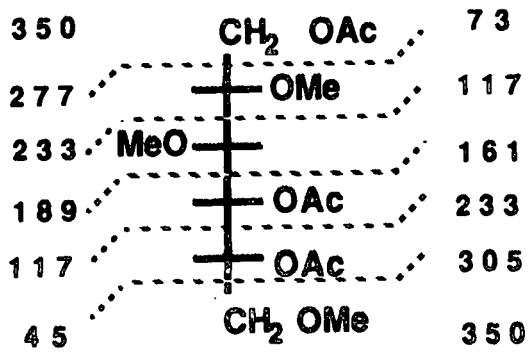


Table 15. Mass spectrum (E1) of 1,4,5-tri-O-acetyl-2,3,6-tri-O-methyl-D-glucitol (70) from methylation-hydrolysis of the polymer-supported model (35).

M/E	Relative Abundance	Assignment
233	35.0	*
189	0.4	*
173	4.9	233 - AcOH
161	8.2	*
159	2.9	
145	0.5	
143	4.7	
142	6.6	
131	11.9	173 - CH_2CO
130	1.5	
129	14.2	161 - MeOH
127	1.9	
117	100.0	*
114	3.5	
113	34.4	
111	2.9	
101	28.5	161 - AcOH
100	3.1	
99	24.3	131 - MeOH
88	5.0	
87	25.1	129 - CH_2CO
85	7.9	
71	7.8	101 - CH_2CO
45	12.1	*
43	65.4	Ac



APPENDIX III

INFRARED SPECTRA

The infrared spectra of the unfunctionalized polystyrene and the polystyrene supported materials prepared in this study were obtained as KBr pellets. These spectra were used mainly as a qualitative tool to show the presence or absence of functional groups.

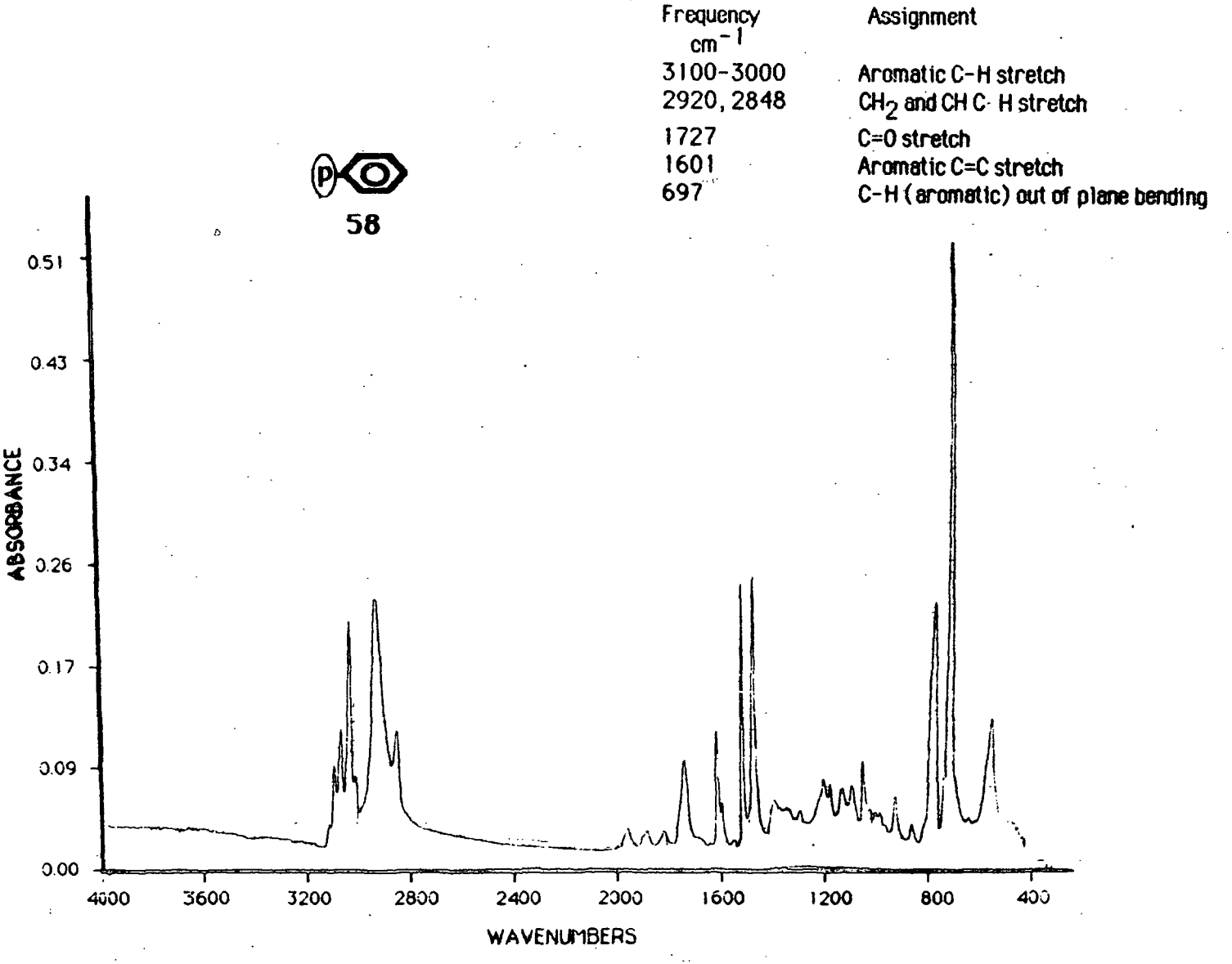


Figure 53. Infrared spectrum of the unfunctionalized polystyrene resin (58).

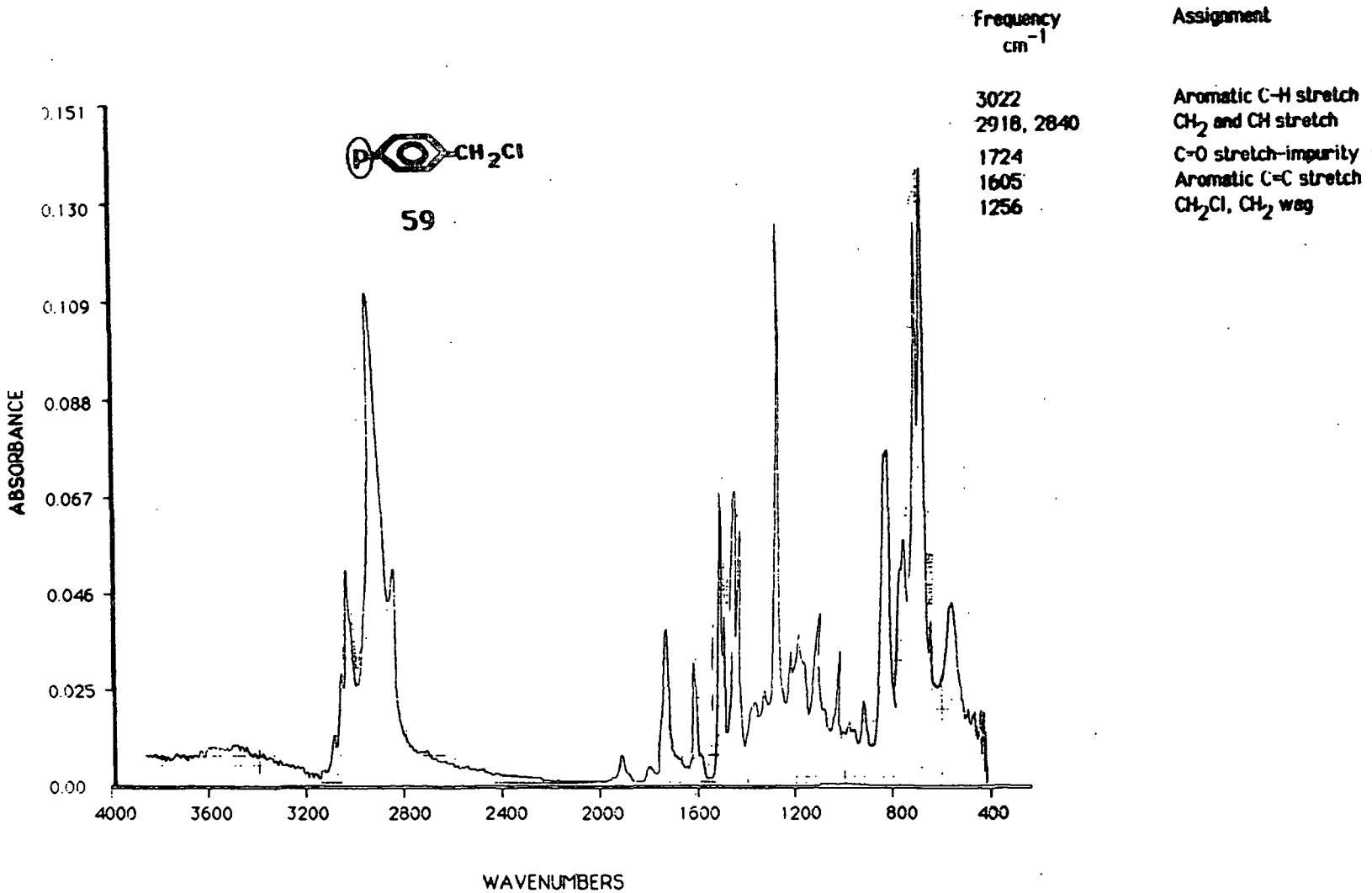


Figure 54. Infrared spectrum of chloromethylated polystyrene resin (59).

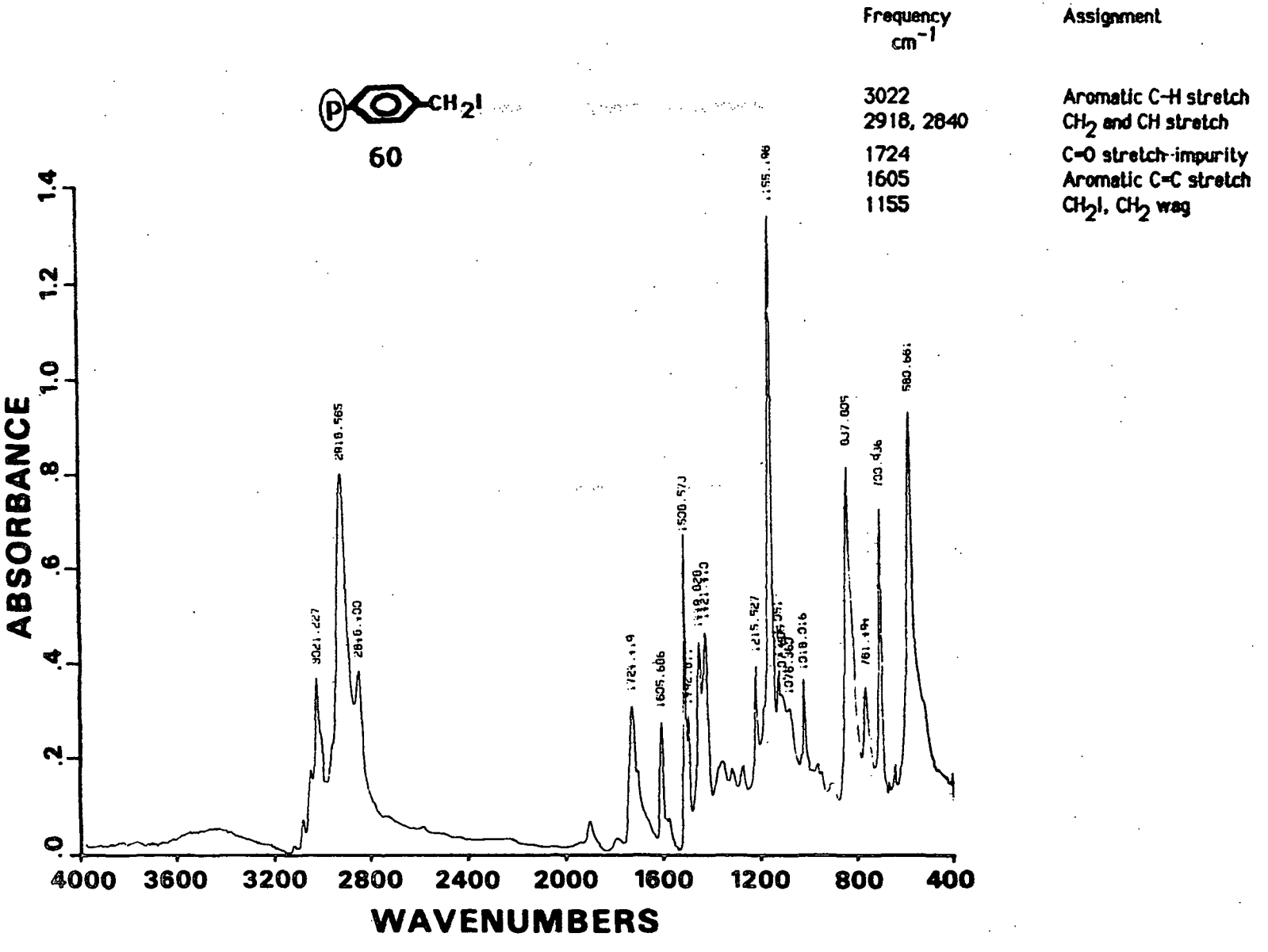


Figure 55. Infrared spectrum of iodomethylated polystyrene resin (60).

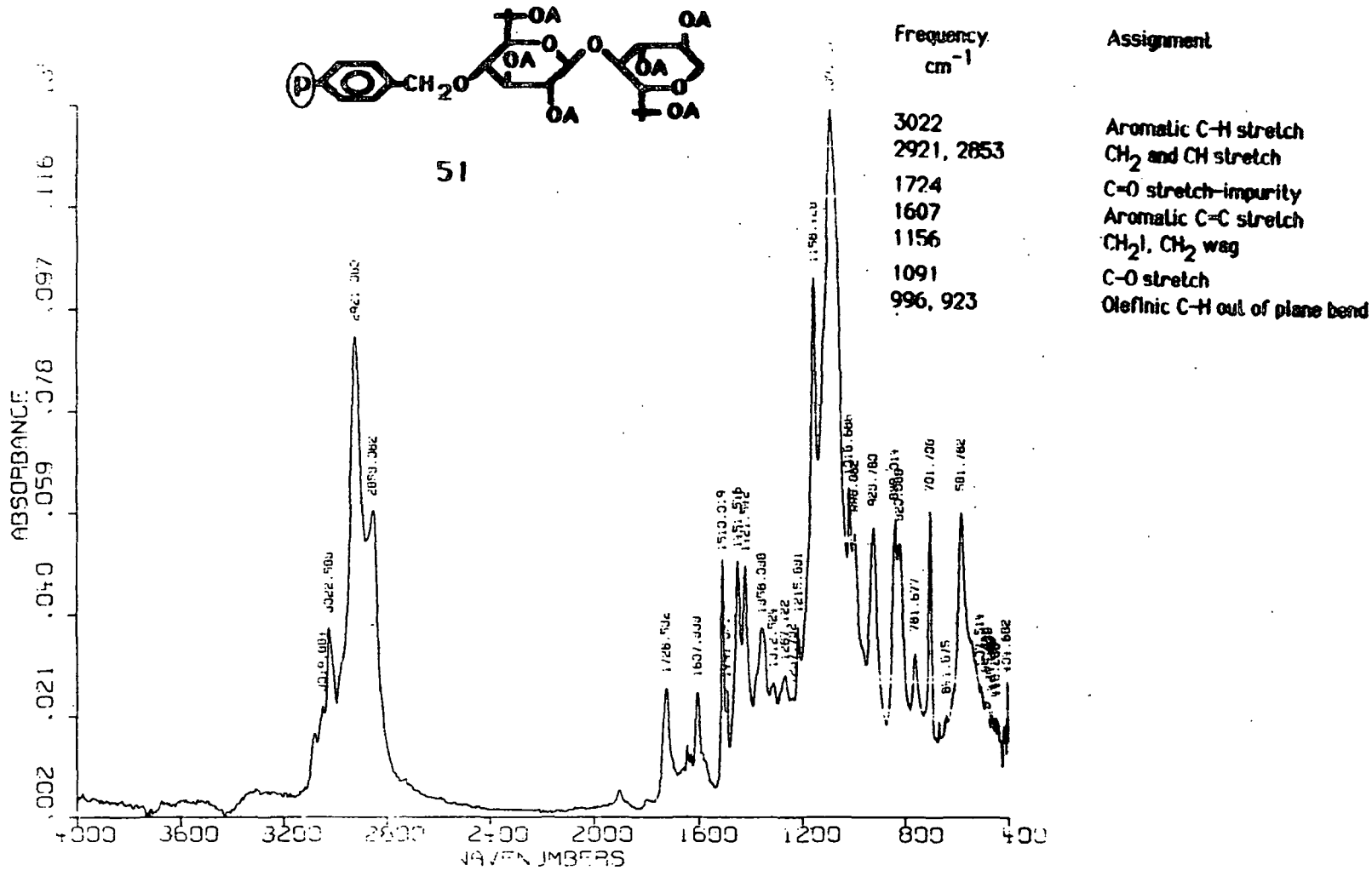


Figure 56. Infrared spectrum of polymer-supported 2,3,6-tri-O-allyl-1,5-anhydro-4-O-(2,3,6-tri-O-allyl-β-D-glucopyranosyl)-D-glucitol (51) prepared in tetrahydrofuran.

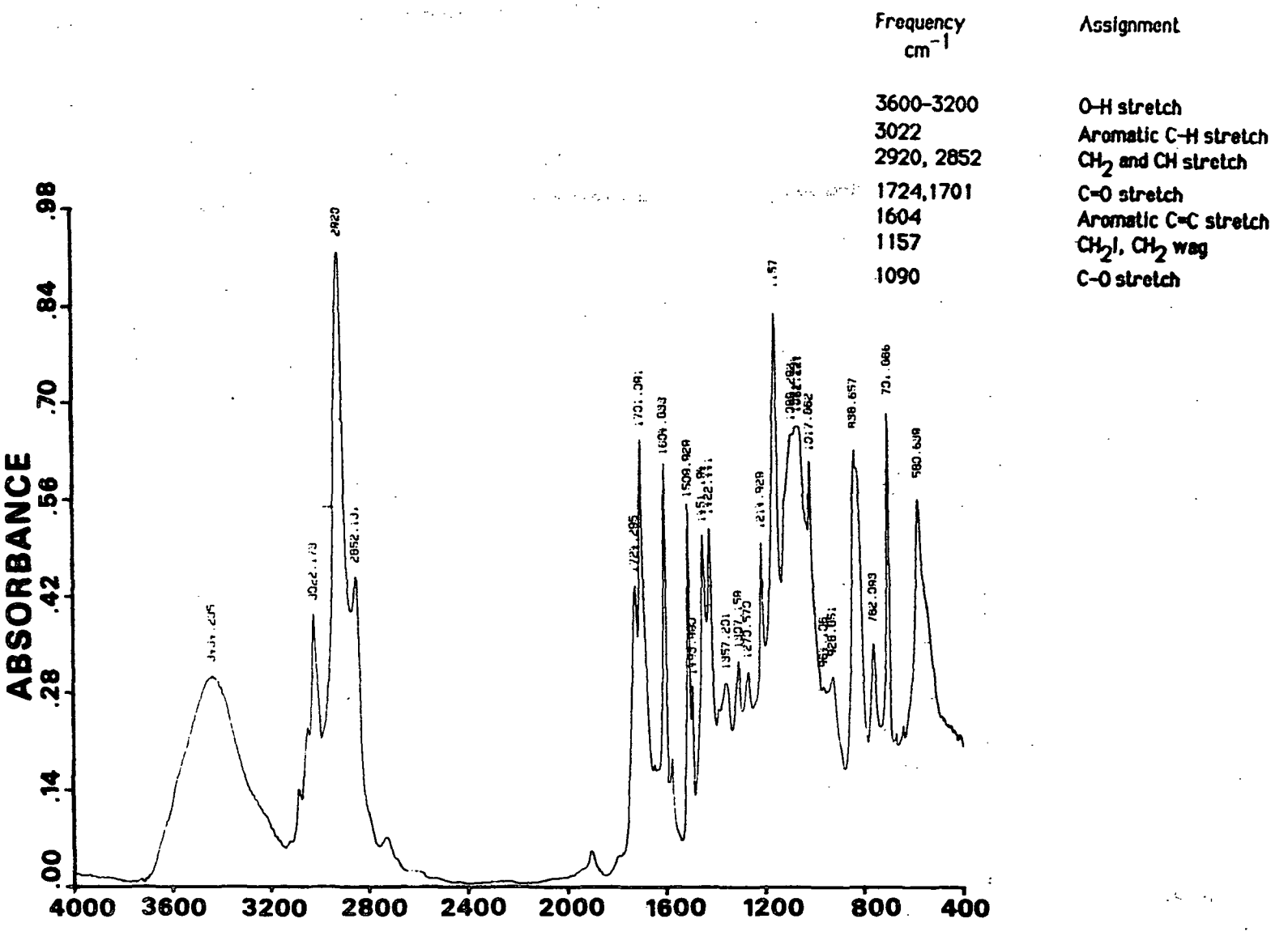


Figure 57. Infrared spectrum of the polystyrene resin recovered from the attempted condensation of 2,3-6-tri-O-allyl-1,5-anhydro-4-O-(2,3,6-tri-O-allyl-β-D-glucopyranosyl)-D-glucitol (50) with iodomethylated polystyrene (60) in dimethyl sulfoxide.

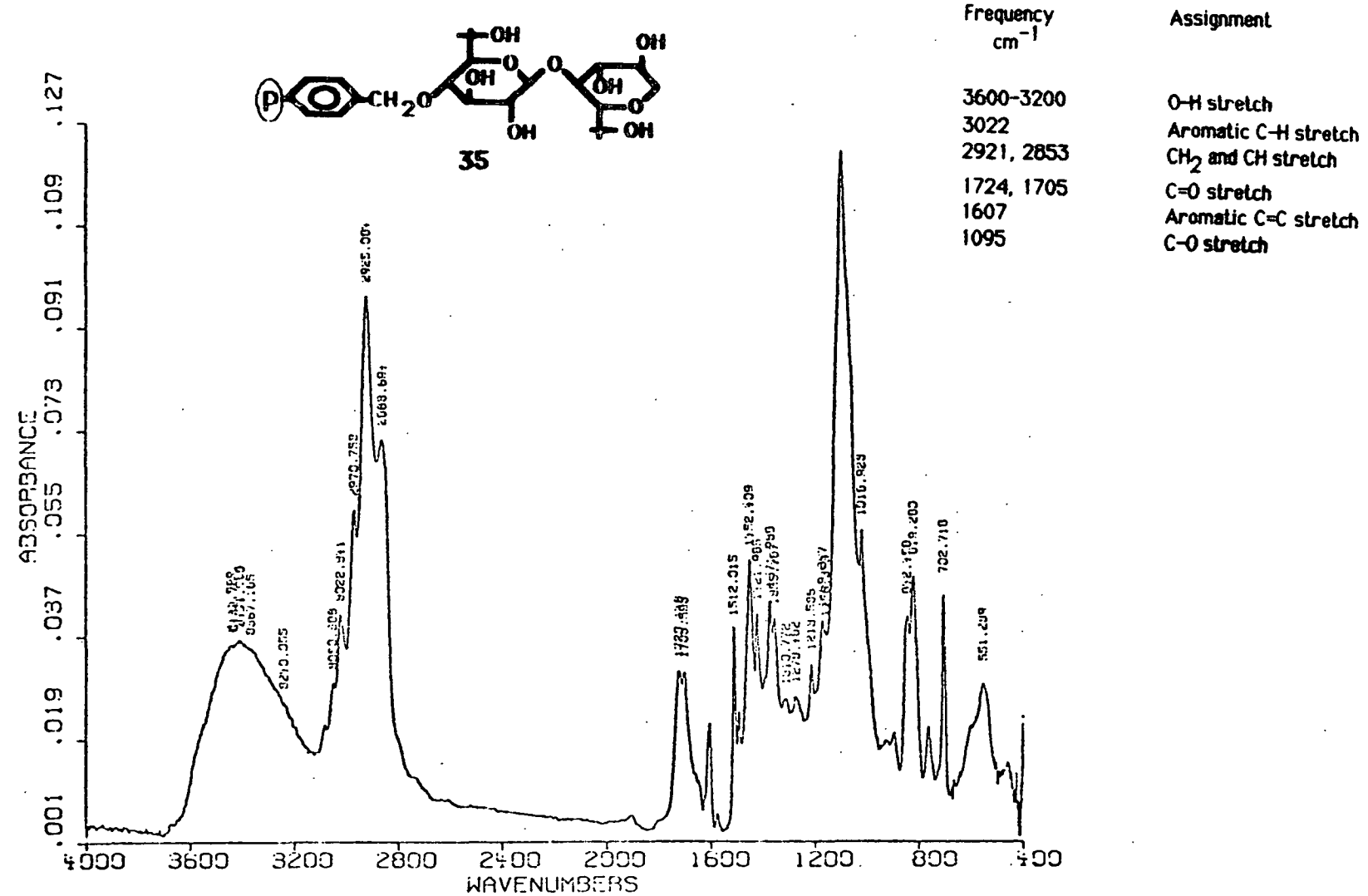


Figure 58. Infrared spectrum of polymer-supported 1,5-anhydrocellobiitol (35).

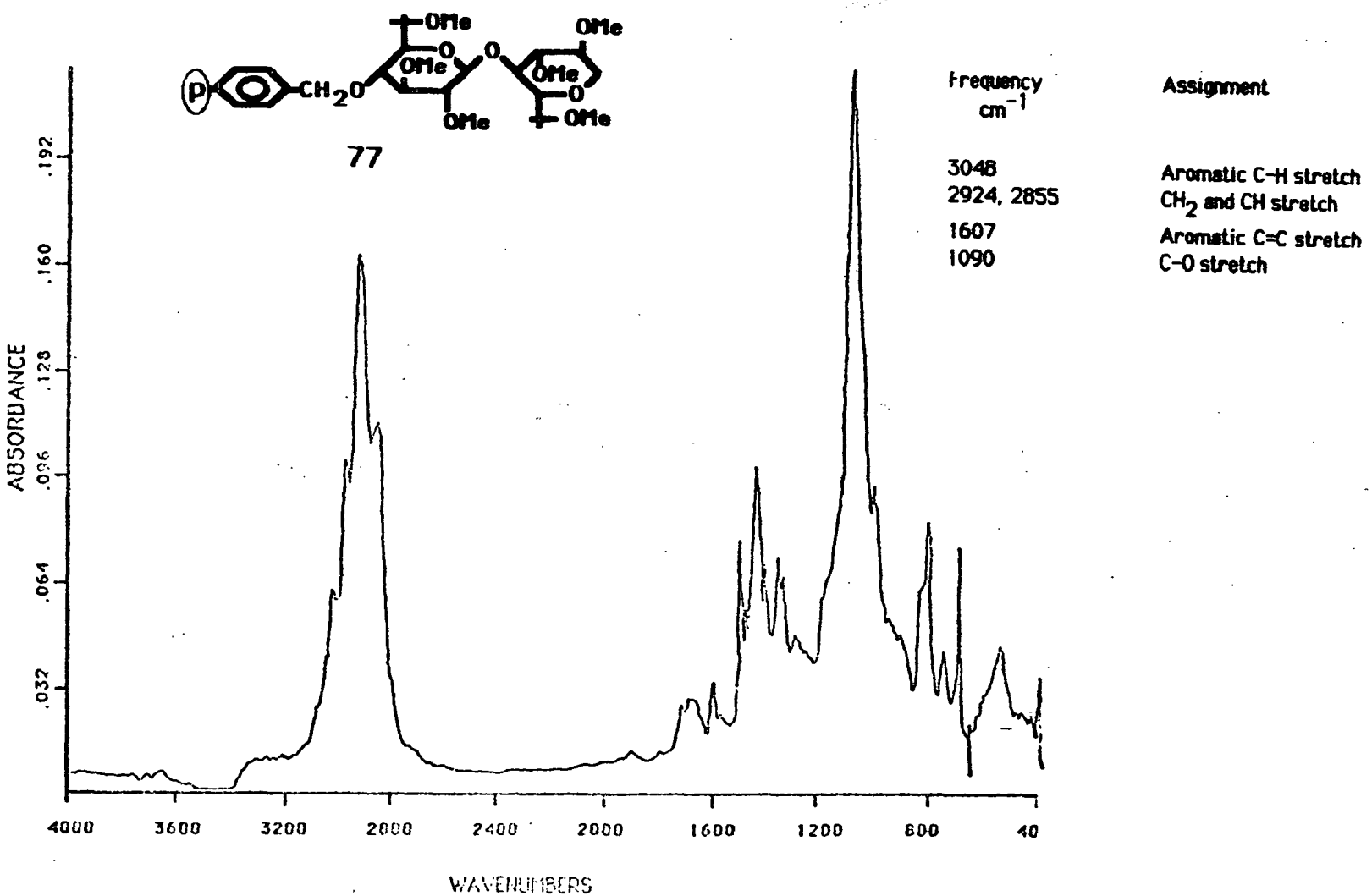


Figure 59. Infrared spectrum of polymer-supported 1,5-anhydro-2,3-6-tri-O-methyl-4-O-(2,3,6-tri-O-methyl-β-D-glucopyranosyl)-D-glucitol (77).

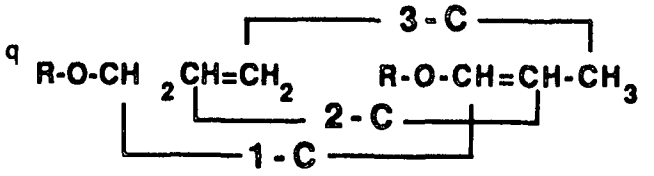
APPENDIX IV

DEALLYLATION

Allyl ethers are removed by base catalyzed rearrangement to the prop-1-enyl ethers and subsequent acid hydrolysis. The rearrangement or isomerization step has been shown to be rapid and quantitative with potassium t-butoxide in dimethyl sulfoxide (DMSO).[82] However, Brimacombe et al.[70] were unable to achieve complete isomerization with potassium t-butoxide-dimethyl sulfoxide. Gigg et al.[83] later repeated Brimacombe's work with satisfactory results. Gigg emphasized the importance of catalyst age, reaction temperature, and reaction time. Brimacombe's difficulties prompted the study of this and other potential deallylation techniques.

The test isomerizations were performed on methyl 2,3,4,6-tetra-O-allyl-α-D-glucopyranoside[57] and followed by ^{13}C-NMR spectroscopy. The major spectral changes consisted of shifts in the ether 1-C^q signal from 70-85 to 145-150 ppm, the 2-C signal from 130-135 to 80-100 ppm, and the 3-C signal from 115-120 to 10-20 ppm (Fig. 61 and 63).

In addition to potassium t-butoxide-dimethyl sulfoxide, allyl groups can be isomerized by the following: (a) sodium metal in liquid ammonia,[84] (b) potassium amide in liquid ammonia,[85] (c) sodium amide in 1,2-dimethoxyethane (DME),[85] (d) palladium on carbon in water,[86] and (e) tristriphenylphosphinerhodium chloride (TPPRC) in aqueous ethanol.[59] Methods a, b, and d were not tested because they could potentially cleave the benzyl ether.



The results, summarized in Table 16, support Gigg's contention that in the potassium t-butoxide-dimethyl sulfoxide system the age of the catalyst is critical. Old potassium t-butoxide gave poor results. Although the isomerization with fresh potassium t-butoxide was successful, the attempt to generate potassium t-butoxide in situ from potassium hydride and t-butanol was not. The reason for this is unclear.

Table 16. Trial isomerizations of allyl ethers.

Base	Solvent	Temperature (°C)	Time (hr)	Degree of Reaction
K-t-OBu[a]	DMSO[b]	100	1	Partial reaction
K-t-OBu[a]	DMSO[b]	100	3	Partial reaction
KH t-butanol	DMSO[b]	100	3	No reaction
$NaNH_2$	DME	20	4	No reaction
K-t-OBu[c]	DMSO[b]	80	2	Complete reaction
TPPRC	H_2O-EtOH-benzene	80	3	Complete reaction

[a]Old K-t-OBu.
[b]Reactions were performed in deuterated dimethyl sulfoxide.
[c]Fresh K-t-OBu.

The hydrolysis of methyl 2,3,4,6-tetra-O-prop-1-enyl-α-D-glucopyranoside with dilute acid proceeded smoothly according to TLC. However, acetylation of the reaction mixture and analysis by GLC indicated two products. The major product accounted for 75% of the reaction and was identified as methyl 2,3,4,6-tetra-O-acetyl-α-D-glucopyranoside by comparison of its retention time with a known sample. The products from a second hydrolysis were separated by column chromatography and analyzed by ^{13}C-NMR spectroscopy. The spectrum of the minor

product indicated formation of a n-propylidene acetal (Fig. 64). In addition to the carbohydrate signals, the spectrum showed a second acetal carbon at 102.3 ppm, a methylene carbon at 27.2 ppm, and a methyl carbon at 8.6 ppm.

The formation of the propylidene may be explained by attack of a neighboring hydroxyl group on the propyl carbonium ion which is generated during the hydrolysis (Fig. 60). The 4,6-O-n-propylidene is the most probable, however other acetals are possible. Similar reactions have been reported. For example, Wolfrom and coworkers[87] prepared 4,6-ethylidene-D-glucopyranose by an acid catalyzed reaction of 4-O-ethylene-D-glucopyranose. The formation of the propylidene was prevented by increasing the water content of the hydrolysis solution.

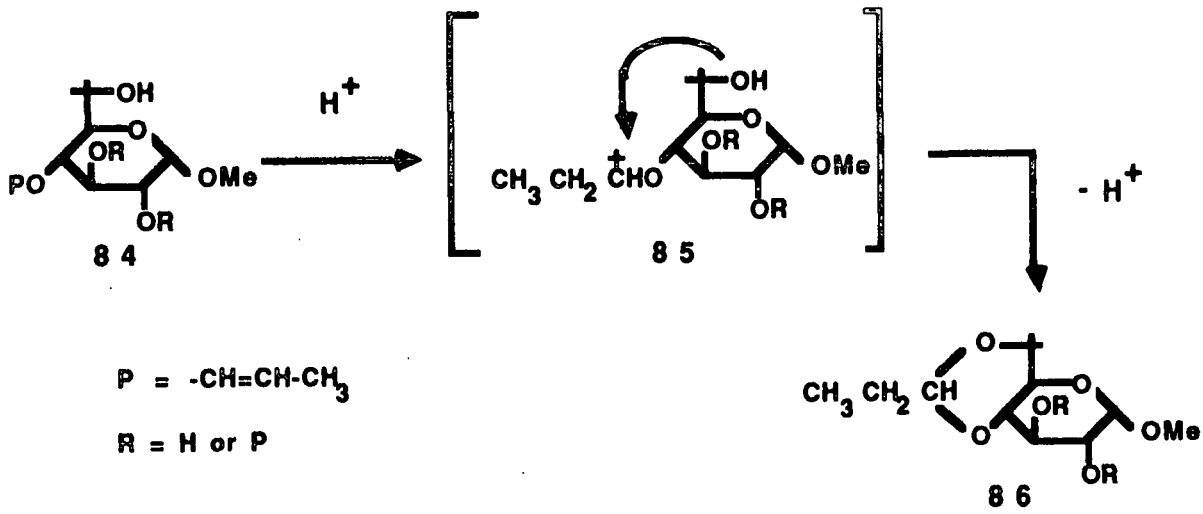
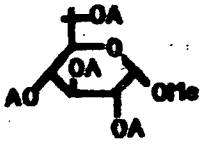


Figure 60. Formation of a n-propylidene acetal from the hydrolysis of prop-1-enyl ethers.

Chemical Shift, ppm	Assignment
134.9	b
134.4	b
134.1	b
117.1	c
116.7	c
116.2	c
116.0	c
97.8	C-1
81.1	a or d
79.1	a or d
78.1	Chloroform
77.0	a or d
75.6	Chloroform
73.9	a or d
73.5	a or d
72.2	a or d
72.1	a or d
69.7	a or d
68.2	a or d
54.7	$-O\underline{C}H_3$
29.5	Dimethylformamide

a b c
$-CH_2-CH=CH_2$

d = C-2, C-3, C-4, C-5, or C-6



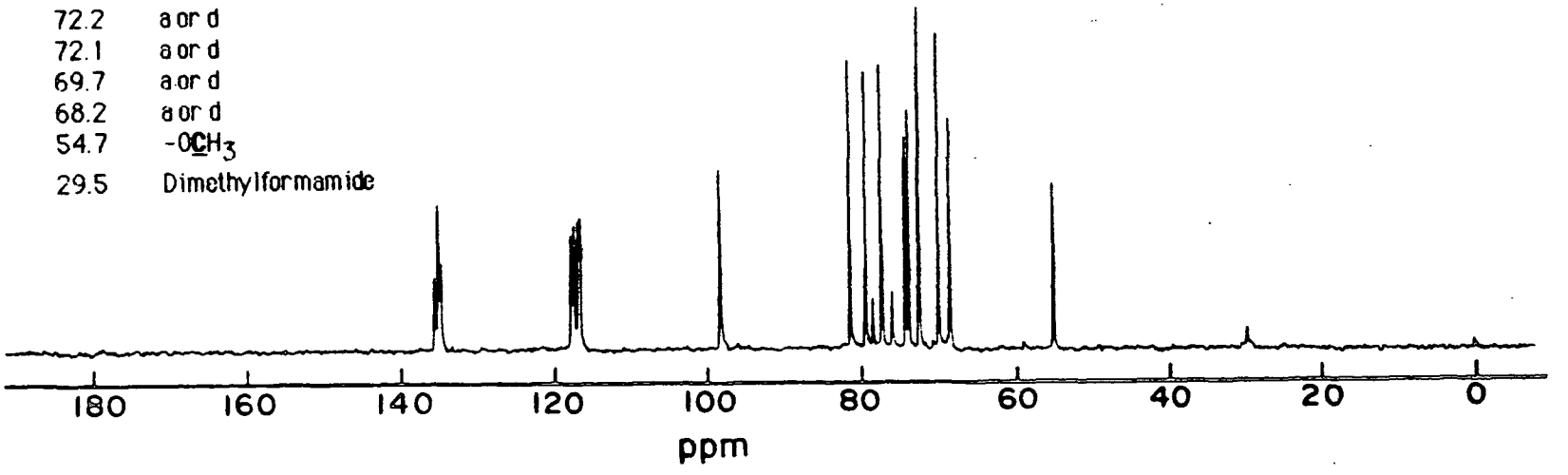


Figure 61. ^{13}C-NMR spectrum of methyl 2,3,4,6-tetra-O-allyl-α-D-glucopyranoside (82) in d-chloroform.

Chemical Shift, ppm	Assignment
148.5	d
148.3	d
148.1	d
147.9	d
137.4	b
118.3	c
102.8	e
102.0	e
101.2	e
99.4	C-1
83.7	a, i or g
82.7	a, i or g
81.5	a, i or g
80.5	a, i or g
75.4	a, i or g
72.1	a, i or g
71.3	a, i or g
68.0	a, i or g
56.5	$-O\underline{C}H_3$
43.5	Dimethyl Sulfoxide
42.7	Dimethyl Sulfoxide
41.8	Dimethyl Sulfoxide
41.0	Dimethyl Sulfoxide
40.2	Dimethyl Sulfoxide
34.8	h
11.4	f

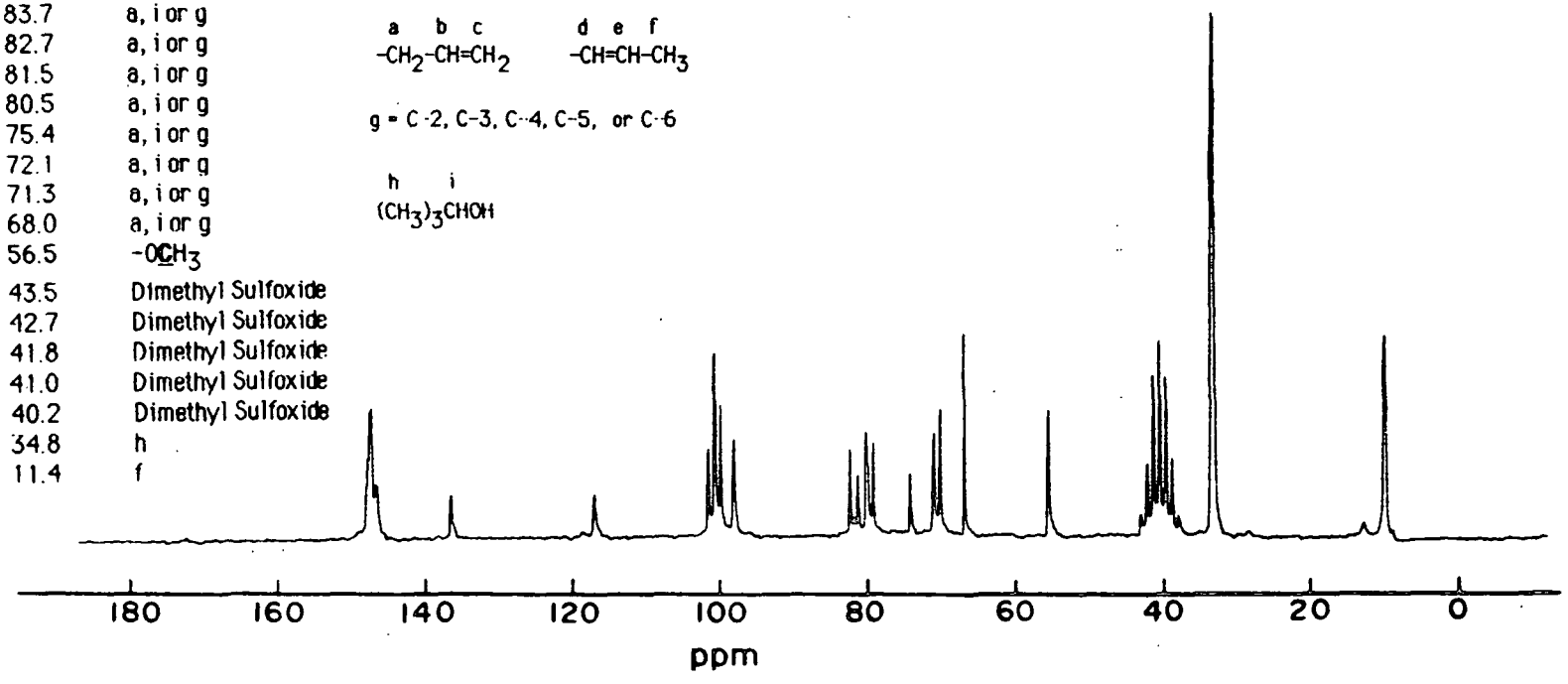


Figure 62. ^{13}C-NMR spectrum of methyl 2,3,4,6-tetra-O-allyl-α-D-glucopyranoside (82) in d-dimethyl sulfoxide after treatment with potassium t-butoxide for one hour at 80°C.

Chemical Shift, ppm	Assignment
148.5	d
148.3	d
148.1	d
147.4	d
137.4	b
118.2	c
102.9	e
102.1	e
101.3	e
99.4	C-1
83.7	a, i or g
81.6	a, i or g
80.5	a, i or g
72.2	a, i or g
71.3	a, i or g
68.1	a, i or g
56.9	$-O\underline{C}H_3$
43.5	Dimethyl Sulfoxide
42.7	Dimethyl Sulfoxide
41.9	Dimethyl Sulfoxide
41.0	Dimethyl Sulfoxide
40.2	Dimethyl Sulfoxide
34.7	h
11.4	f

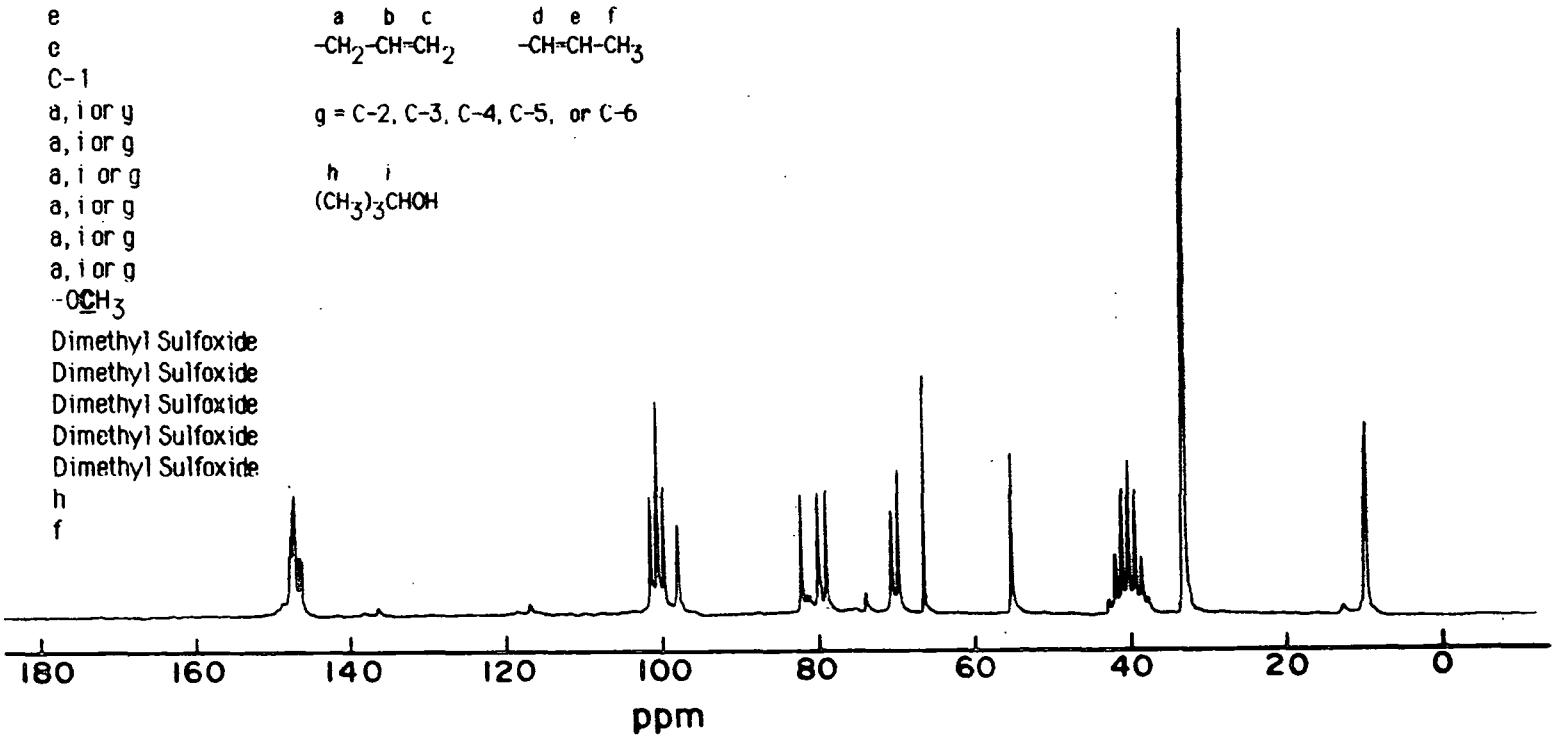


Figure 63. ^{13}C-NMR spectrum of methyl 2,3,4,6-tetra-O-allyl-α-D-glucopyranoside (82) in d-dimethyl sulfoxide after treatment with potassium t-butoxide for two hours at 80°C.

Chemical Shift, ppm	Assignment
102.3 (d)	a
100.5 (d)	C-1
80.9 (d)	d
72.5 (d)	d
70.0 (d)	d
67.8 (t)	C-6
62.5 (d)	d
54.7 (q)	$-O\underline{C}H_3$
40.4	Dimethyl Sulfoxide
39.5	Dimethyl Sulfoxide
38.7	Dimethyl Sulfoxide
27.2 (t)	b
8.6 (q)	c

a b c

$(RO)_2CH-CH_2-CH_3$

d = C-2, C-3, C-4, or C-5

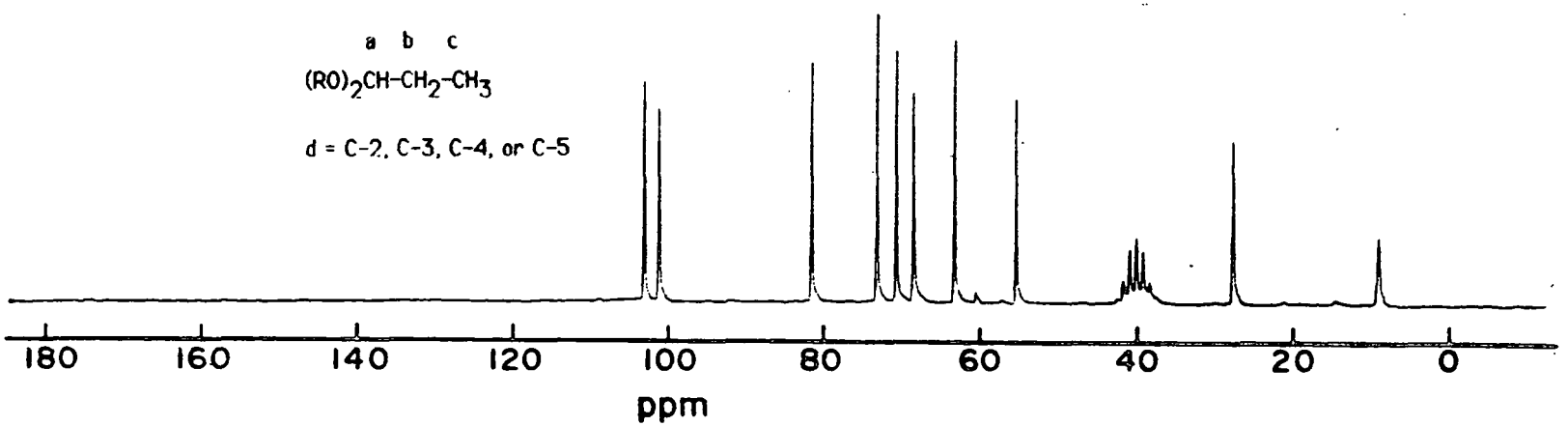


Figure 64. ^{13}C-NMR spectrum of the unknown product from the acid hydrolysis of methyl 2,3,4,6-tetra-O-prop-1-enyl-α-D-glucopyranoside (83).